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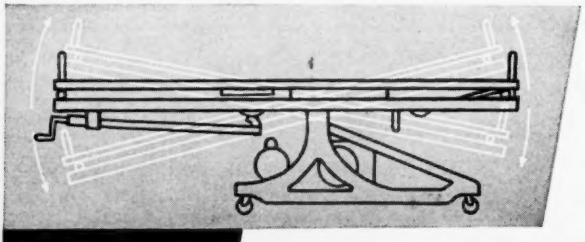

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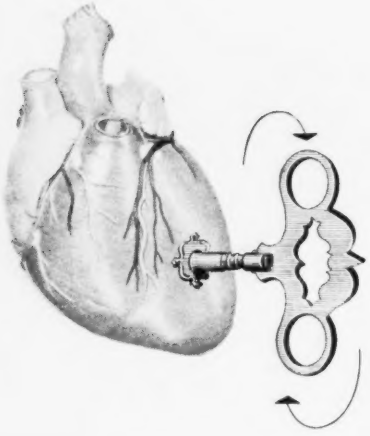

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ROLE OF BLOOD PLATELETS IN THROMBOEMBOLISM

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AND

BETTY GOODMAN

NEW BRUNSWICK, N. J.

DEVELOPMENT OF MODERN CONCEPTS OF THROMBUS FORMATION

IN THE first half of the nineteenth century, thrombosis of blood vessels was held to result either from excessive coagulability of the blood or from exudative inflammation of the vascular wall. Virchow's views [1] influenced subsequent thought on the subject of intravascular clotting by their stress on the importance of slowing or stagnation of blood flow as well as on altered "molecular attraction" between the blood and the vascular wall.

By means of experiments in living animals, Mantegazza [2] (1869, 1871) and Zahn [3] (1875) assembled proof that thrombosis is not equivalent to simple clot formation but consists primarily in a process of selective precipitation of protoplasmic elements from the flowing blood at sites of vascular injury to form a homogeneous, grayish white deposit (the "white thrombus"). With complete occlusion of the lumen by the white thrombus, the blood which is trapped in a column quickly clots to form a cast of the vessel (the "red thrombus"). The same principle (formation of an occlusive white thrombus followed by clotting of whole blood) was shown to hold also for the closure of puncture defects in veins (Zahn [3]).

From the Research Division, Laboratory Service, St. Peter's General Hospital.

This study was aided by grants from the Dazian Foundation, Dr. F. M. Clarke and Mr. Harry Hillman.

1. Virchow, R.: Gesammelte Abhandlungen zur wissenschaftlichen Medicin. Frankfurt a. M., Meidinger Sohn u. Comp., 1856; cited by Eberth, J. C., and Schimmelbusch, C.: Experimentelle Untersuchungen über Thrombose, Virchows Arch. f. path. Anat. **103**:39, 1886; **105**:331 and 456, 1886.

2. Mantegazza, cited by Bizzozero, J.: Ueber einen neuen Formbestandtheil des Blutes und dessen Rolle bei der Thrombose und der Blutgerinnung, Virchows Arch. f. path Anat. **90**:261, 1882.

3. Zahn, F. W.: Untersuchungen über Thrombose: Bildung der Thromben, Virchows Arch. f. path. Anat. **62**:81, 1875.

Through Bizzozero's epochal investigations [4] (1882), the mammalian blood platelets were properly classified and their key position in thrombosis was firmly established. Employing a technic of direct observation of the vessels in the guinea pig omentum he repeated experiments of Jones [5] (1850), Mantegazza [2] and Zahn [3] and proved that the white thrombi which form at sites of mechanical or chemical injury are composed principally of agglutinated platelets which gradually become fused into a granular viscous substance. Clotting occurs in the wake of the changes in the platelets. Agents which prevent or retard blood clotting were found to inhibit platelet alteration. Bizzozero noted further that fibrin is deposited in a blood vessel only when platelets have previously become attached to its lining.

Osler,[6] who had also studied the clumping of platelets, reported them to be the chief component of vegetations on cardiac valves and of mural thrombi of the aorta or of aortic aneurysms. Hayem,[7] at about the same time, established the importance of platelets in the arrest of hemorrhage. They were shown to form an effective hemostatic plug by their agglutination to the edges of a vascular defect in advance of clotting.

Later workers [8] confirmed these data and extended knowledge in several directions. It has become a commonplace observation that agents which inhibit clotting also suppress or delay platelet adhesiveness, agglutination and lysis,[9] retard thrombus formation [10] and may impair

4. Bizzozero, J.: Ueber einen neuen Formbestandtheil des Blutes und dessen Rolle bei der Thrombose und der Blutgerinnung, Virchows Arch. f. path. Anat. **90**:261, 1882.

5. Jones, T. W.: On the State of the Blood and the Blood-Vessels in Inflammation, Ascertained by Experiments, Injections, and Observations by the Microscope, Guy's Hosp. Rep. **7**:1, 1851.

6. Osler, W.: Ueber den dritten Formbestandtheil des Blutes, Centralbl. f. d. med. Wissensch. **20**:529, 1882; On Certain Problems in the Physiology of the Blood Corpuscles, M. News **48**:365, 393 and 421, 1886.

7. Hayem, G.: Sur le mécanisme de l'arrêt des hémorrhagies, Compt. rend. Acad. d. sc. **95**:18, 1882.

8. (*a*) Schimmelbusch, C.: Die Blutplättchen und die Blutgerinnung, Virchows Arch. f. path. Anat. **101**:201, 1885. (*b*) Eberth, J. C., and Schimmelbusch, C.: Experimentelle Untersuchungen über Thrombose, ibid. **103**:39, 1886; **105**:331 and 456, 1886. (*c*) Welch, W. H.: Thrombosis, in Albutt, T. C.: A System of Medicine, London, Macmillan & Co., 1899, vol. 7, p. 155; reprinted in Papers and Addresses, Baltimore, Johns Hopkins Press, 1920, vol. 1, p. 110. (*d*) Aschoff, L.: Thrombosis, in Lectures on Pathology, New York, Paul B. Hoeber, 1924, chap. 11; Thrombose und Embolie, Verhandl. d. deutsch. Gesellsch. f. Kreislaufforsch. 1934, p. 11.

9. (*a*) Bizzozero.[4] (*b*) Bürker, K.: Blutplättchen und Blutgerinnung, Arch. f. d. ges. Physiol. **102**:36, 1904. (*c*) Aynaud, M. N.: Le globulin des mammifères, Thesis, Paris, no. 93, 1909. (*d*) Deetjen, H.: Zerfall und Leben der Blutplättchen,

hemostasis.[11] As a corollary, it is also accepted by many authorities that thrombus formation as well as hemostasis depends not only on the availability of a sufficient number of platelets [12] but also on their capacity to adhere and to undergo lysis.[13]

ROLE OF PLATELETS IN VASCULAR PHYSIOLOGY

The normal rate of formation and destruction of platelets has not been determined accurately. After marked reduction in their number, one third of the entire normal amount can be regenerated in twenty-four

Ztschr. f. phys. Chemie **63**:1, 1909. (*e*) Ferguson, J. H.: The Blood Calcium and the Calcium Factor in Blood Coagulation, Physiol. Rev. **16**:640, 1936. (*f*) Fonio, A., and Schwendener, J.: Die Thrombozyten des menschlichen Blutes und ihre Beziehung zum Gerinnungs- und Thrombosevorgang, Bern, Hans Huber, 1942. (*g*) Tocantins, L. M.: The Mammalian Blood Platelets in Health and Disease, Medicine **17**:155, 1938. (*h*) Wright, H. P.: The Adhesiveness of Blood Platelets in Normal Subjects with Varying Concentrations of Anti-Coagulants, J. Path. & Bact. **53**:255, 1941. (*i*) The Adhesiveness of Platelets in Rabbits Treated with Dicoumarol, ibid. **57**:382, 1945. (*j*) Jürgens, R.: Blutstillungsregulationen unter dem Einfluss von Blutegelextrakt, Ztschr. f. d. ges. exper. Med. **63**:74, 1928. (*k*) Quick, A. J.: The Hemorrhagic Diseases and the Physiology of Hemostasis, Springfield, Ill., Charles C Thomas, Publisher, 1942. (*l*) Rosenthal, N.: Blood Platelets and Megakaryocytes, in Downey, H.: Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1938, vol. 1, sect. 7. (*m*) Roskam, J.: Physiologie normale et pathologique du globulin (Plaquette de Bizzozero), Paris, Presses Universitaires de France, 1927.

10. (*a*) Apitz, K.: Ueber den Bau jüngster Blutplättchenthromben und den Einfluss des Novirudins auf ihre Entstehung, Centralbl. f. allg. Path. u. path. Anat. **50**:9, 1930. (*b*) Best, C. H.; Cowan, C., and Maclean, D. L.: Heparin and the Formation of White Thrombi, J. Physiol. **92**:20, 1938. (*c*) Zucker, M. B.: Platelet Agglutination and Vasoconstriction as Factors in Spontaneous Hemostasis in Normal, Thrombocytopenic, Heparinized and Hypoprothrombinemic Rats, Am. J. Physiol. **148**:275, 1947. (*d*) Dale, D. U., and Jaques, L.: The Prevention of Experimental Thrombosis by Dicoumarin, Canad. M. A. J. **46**:546, 1942.

11. (*a*) Jürgens.[9j] (*b*) Zucker.[10c] (*c*) Dale and Jaques.[10d] (*d*) Jürgens, R.: Beitrag zur Pathologie und Klinik der Blutungsbereitschaft, Ztschr. f. klin. Med. **123**:649, 1933.

12. (*a*) Hayem.[7] (*b*) Welch.[8c] (*c*) Aschoff.[8d] (*d*) Quick.[9k] (*e*) Frank, E.: Hämorrhagische Diathesen, in Klemperer, G., and Klemperer, F.: Neue deutsche Klinik, Berlin, Urban & Schwarzenberg, 1930, vol. 4, p. 935.

13. (*a*) Jürgens.[11d] (*b*) Baar, H., and Székely, L.: Über die Plättchenzerfallsgeschwindigkeit bei normalen Kindern, bei der Hämophilie und Thrombopenie, Ztschr. f. Kinderh. **48**:31, 1929. (*c*) Baar, H.: The Stickiness of Platelets, Lancet **2**:775, 1941. (*d*) Wright, H. P.: Changes in the Adhesiveness of Blood Platelets Following Parturition and Surgical Operations, J. Path. & Bact. **54**:461, 1942. (*e*) Silberberg, M.: The Causes and Mechanism of Thrombosis, Physiol. Rev. **18**:197, 1938. (*f*) Aggeler, P. M.; Howard, J., and Lucia, S. P.: Platelet Counts and Platelet Function, Blood **1**:472, 1946. (*g*) Jürgens, R., and Naumann, W.: Klinische und experimentelle Untersuchungen über Funktionen der Blutplättchen, Deutsches Arch. f. klin. Med. **172**:248, 1931. (*h*) Tocantins, L. M.: The Mechanism of Hemostasis, Ann. Surg. **125**:292, 1947. (*i*) Apitz, K.: Die Dukesche Probe, Ztschr. f. d. ges. exper. Med. **111**:554, 1942.

hours.[9g] According to Tocantins,[14] the principal site of platelet destruction is the peripheral circulation. Evidence exists that the platelets may be physiologically concerned in controlling capillary permeability to water and plasma proteins (Danielli[15]). Vasoconstrictor activity has also been shown to occur in the products of platelet lysis and has been credited with an important role in hemostasis.[16] In idiopathic thrombopenic purpura, the fragile, toneless, overfilled capillaries (Macfarlane[17]) and the wide differences in bleeding time in various parts of the body (Roskam[9m]) may reflect not only a numerical lack of platelets but reduced platelet lysis (Reid,[16e] Zucker[10c]) and defective biologic activity as well. As a corollary, there is the possibility that platelet lysis in the peripheral circulation plays a physiologic role in the normal contractility and tonus of the minute vessels (the precapillaries and venules). The labile character and activity of the platelets even more than their quantity may thus determine to an important degree the functional state of these vessels as measured by tests of bleeding time and capillary fragility. As once stated by Howell and Donahue,[18] the megakaryocyte "constitutes, so to speak, a unicellar gland which gives off a solid secretion in the form of platelets. The eventual solution or disintegration of the platelets presumably adds to the plasma important constituents. . . ."

Recently, Zucker[10c] imparted experimental evidence indicating that platelet vasoconstrictor substance is liberated rapidly from white thrombi and, by its diffusion locally, causes vasoconstriction within a considerable area. According to Reid,[19] this agent may be a factor, if not the sole factor, in maintaining vasoconstriction in the peripheral field

14. Tocantins, L. M.: Arterial, Venous and Cutaneous Blood Platelet Counts in Men and Dogs Under Normal and Abnormal Conditions, Am. J. M. Sc. **192**:150, 1936.

15. Danielli, J. F.: Capillary Permeability and Oedema in the Perfused Frog, J. Physiol. **98**:109, 1940.

16. (*a*) Zucker.[10c] (*b*) O'Connor (1912); Zucker and Stewart (1913); Janeway, Richardson and Park (1918); Freund (1920) and Reid and Bick (1942), cited by Zucker, M. B.: A Study of the Substances in Blood Serum and Platelets Which Stimulate Smooth Muscle, Am. J. Physiol. **142**:12, 1944. (*c*) Feissly, cited by Roskam.[9m] (*d*) Zucker, M. B.: A Study of the Substances in Blood Serum and Platelets Which Stimulate Smooth Muscle, Am. J. Physiol. **142**:12, 1944. (*e*) Reid, G.: A Preliminary Note on the Relationship of the Blood Platelets to the Mechanism of Hæmostasis, M. J. Australia **2**:244, 1943.

17. Macfarlane, R. G.: Critical Review: The Mechanism of Haemostasis, Quart. J. Med. **10**:1, 1941.

18. Howell, W. H., and Donahue, D. D.: The Production of Blood Platelets in the Lungs, J. Exper. Med. **65**:177, 1937.

19. Reid, G.: Observations on the Part Played by the Vasoconstrictor Substance of Blood Platelets in the Mechanism of Vascular Spasm, M. J. Australia **2**:139, 1947.

of an artery damaged, thrombosed or occluded by an embolus, provided the circulation is inadequate to remove it or it continues to be liberated. It is also conceivable that the platelet vasoconstrictor agent accounts for the arterial spasm which frequently complicates thrombophlebitis and which is commonly regarded [20] as a reflex originating in the inflamed venous wall.

PLATELET AGGLUTINATION AND ADHESIVENESS

The formation of blood platelets from ripened megakaryocytes of the bone marrow has been shown to depend on a process of partitioning occurring first in the cytoplasmic granules [21] and later completed in the cytoplasm itself.[22] The individual platelets, formed in this manner, exhibit a remarkable tendency to remain dispersed in the normal circulation.[23] Even after being crowded in the spleen, they may be liberated therefrom in large numbers after the injection of epinephrine (adrenalin®) and may remain separate from one another and free of any increased tendency to clump or adhere.[24]

Under certain conditions, the platelets lose suspension stability [25] more readily even than erythrocytes or leukocytes [8b] and clump rapidly with one another or on a favored surface. Factors in platelet agglutination are held to include (1) intrinsic changes in their protoplasm, probably lytic in character,[26] which render them more susceptible to the "spreading" action of a wettable surface [27] and (2) changes in the surrounding blood plasma which favor clumping of suspended particles. The plasmatic changes are said to include an increase in electronegative plasma proteins (globulins and fibrinogen), which partially cancels the negative charge on the surface of the platelets and so reduces the mutual repulsion which exists between them, as in the

20. Ochsner, A., and DeBakey, M.: Thrombophlebitis: The Role of Vasospasm in the Production of the Clinical Manifestations, J. A. M. A. **114**:117 (Jan. 13) 1940.

21. Seeliger, cited by Frank, E.: Die hämorrhagischen Diathesen, in Schittenhelm, A.: Enzyklopädie der inneren Medizin, Handbuch der Krankheiten des Blutes und der blutbildenden Organe, Berlin, Julius Springer, 1925, vol. 2, p. 289.

22. Dameshek, W., and Miller, E. B.: The Megakaryocytes in Idiopathic Thrombocytopenic Purpura: A Form of Hypersplenism, Blood **1**:27, 1946.

23. Osler.[6] Schimmelbusch.[8a] Eberth and Schimmelbusch.[8b]

24. Wright, H. P.: The Sources of Blood Platelets and Their Adhesiveness in Experimental Thrombocytosis, J. Path. & Bact. **56**:151, 1944.

25. Osler.[6] Aynaud.[9c] Tocantins.[9g]

26. Bizzozero.[4] Deetjen.[9d] Silberberg.[13e]

27. (*a*) Tait, J., and Elvidge, A. R.: Effect upon Platelets and on Blood Coagulation of Injecting Foreign Particles into the Blood Stream, J. Physiol. **62**:129, 1926. (*b*) Tait, J., and Burke, H. E.: Platelets and Blood Coagulation, Quart. J. Exper. Physiol. **16**:129, 1926; cited by Tait and Elvidge.[27a]

case of all particles carrying a like charge.[28] A similar mechanism is implied in Roskam's idea that a pellicle of plasma protein, including fibrin, "opsonizes" the platelets and the surfaces to which they adhere.[29]

Since the time of Bizzozero, it has become generally recognized that conditions which cause platelets to adhere are essentially the same as those which initiate blood clotting, viz., contact with a "wettable" surface[30] or with injured tissue.[31] It has also become clear that such conditions can influence platelets much more readily than they can provoke clotting.[32] This is demonstrable, for example, in the fact that "white thrombi" appear before "red thrombi" in thrombotic disease of large vessels.[8c] Another example is found in the fact that a plug of agglutinated platelets (*clou hémostatique*) often seals the gap in an injured small vessel well in advance of clotting so that that process serves merely as secondary reenforcement against renewed bleeding.[33] Additional evidence is the fact that in the living animal distinctly larger concentrations of heparin sodium or dicumarol® must be provided to inhibit formation of a white thrombus than to render the animal's blood incoagulable for many hours under experimental conditions which ordinarily result in thrombosis.[34]

Although it is not yet conclusively proved, it is likely that thrombin is the plasmatic factor primarily responsible for intrinsic alterations in blood platelets which result in their acquisition of "stickiness," in their agglutination and in their eventual complete dissolution.[35] Amounts of

28. Starlinger, W., and Sametnik, S.: Ueber die Entstehungsbedingungen der spontanen Venenthrombose, Klin. Wchnschr. **6**:1269, 1927.

29. Roskam, J.: (*a*) footnote 9*m*; (*b*) Le rôle du plasma dans l'agglutination des globulins (plaquettes), Compt. rend Soc. de biol. **86**:733, 1922.

30. (*a*) Bizzozero.[4] (*b*) Haydem.[7] (*c*) Footnote 9 *d*, *e*, *f* and *k*. (*d*) Tait and Elvidge.[27a] (*e*) Tait and Burke.[27b] (*f*) Lampert, H.: Die physikalische Seite des Blutgerinnungsproblems und ihre praktische Bedeutung, Leipzig, Georg Thieme, 1931. (*g*) Aschoff, cited by Lampert.[30f] (*h*) Vulpain (1873), cited by Rosenthal.[91]

31. Mantegazza.[2] Zahn.[3] Bizzozero.[4] Jones.[5] Osler.[6] Hayem.[7] Aynaud.[8c] Fonio and Schwendener.[9f]

32. Bizzozero.[4] Hayem.[7] Schimmelbusch.[8a]

33. Zahn.[3] Hayem.[7]

34. (*a*) Solandt, D. Y., and Best, C. H.: Time-Relations of Heparin Action on Blood-Clotting and Platelet Agglutination, Lancet **1**:1042, 1940. (*b*) Shionoya, T.: Studies in Experimental Extracorporeal Thrombosis: III. Effects of Certain Anticoagulants (Heparin and Hirudin) on Extracorporeal Thrombosis and on the Mechanism of Thrombus Formation, J. Exper. Med. **46**:19, 1927.

35. (*a*) Fonio and Schwendener.[9f] (*b*) Quick, A. J.: Studies on the Enigma of the Hemostatic Dysfunction of Hemophilia, Am. J. M. Sc. **214**:272, 1947. (*c*) Eagle, H.: Recent Advances in the Blood Coagulation Problem, Medicine **16**:95, 1937. (*d*) Ferguson, cited by Eagle.[35c] (*e*) Bessis, M., and Burnstein, M.: Études sur la physiologie des thrombocytes (Revue générale et travaux personnels), Rev. d'hémat. **3**:69, 1948.

thrombin much too small to catalyze the conversion of fibrinogen into fibrin have been found sufficient to affect platelets in vitro.[9f] Quick [35b] postulated the occurrence during clotting of a chain reaction in which lysis, initiated by minute amounts of thrombin, liberates enzymic material from platelets; the material, in turn, catalyzes the formation of active thromboplastin from a precursor of thromboplastin in plasma, resulting in the very rapid conversion of prothrombin into thrombin. The concept of a chain reaction involving thrombin formation explains rather effectively the accelerating effect of blood platelets on blood coagulation [36] as well as their rapid agglutination and lysis in large numbers during the same process.

ROLE OF ENDOTHELIAL CHANGES IN THROMBOSIS

Since Virchow's time, most writers on the subject of thrombosis have accepted the theory that three factors are involved: (1) changes in the composition of the circulating blood, such as increased coagulability or increased platelet count and agglutinability; (2) injury of the vessel wall, which results in the liberation of thromboplastin from tissue or favors the deposition of platelets on an altered surface, and (3) abnormalities of blood flow, which favor the coagulation of blood or the sedimentation of platelets. The evidence which incriminates endothelial injury has been largely experimental, such as the induction of thrombosis by injury (mechanical,[37] chemical [38] or thermal [39]) of either the

36. (*a*) Milstone, J. H.: Activation of Prothrombin by Platelets Plus Globulin, Proc. Soc. Exper. Biol. & Med. **68**:225, 1948. (*b*) Ware, A. G.; Fahey, J. L., and Seegers, W. H.: Platelet Extracts, Fibrin Formation and Interaction of Purified Prothrombin and Thromboplastin, Am. J. Physiol. **154**:140, 1948. (*c*) Eagle, H.: Studies on Blood Coagulation: I. The Role of Prothrombin and of Platelets in the Formation of Thrombin, J. Gen. Physiol. **18**:531, 1935.

37. (*a*) Mantegazza.[2] (*b*) Zahn.[3] (*c*) Bizzozero.[4] (*d*) Jones.[5] (*e*) Hirsch, E., and Loewe, L.: A Method for Producing Experimental Venous Thrombosis, Proc. Soc. Exper. Biol. & Med. **63**:569, 1946. (*f*) Hayem, G.: L'Hématoblaste: troisième élément du sang, Paris, Presses Universitaires de France, 1923. (*g*) Rabinovitch, J., and Pines, B.: The Effect of Heparin on Experimentally Produced Venous Thrombosis, Surgery **14**:669, 1943. (*h*) Murray, D. W. G.; Jaques, L. B.; Perrett, T. S., and Best, C. H.: Heparin and the Thrombosis of Veins Following Injury, ibid. **2**:163, 1937. (*i*) Morton, C. B.; Shearburn, E. W., and Burger, R. E.: Synthetic Vitamin K and the Thrombosis of Veins Following Injury, ibid. **14**:915, 1943. (*j*) Kristenson, A.: Beobachtungen über die Anzahl der Thrombozyten bei experimentell an Kaninchen hervorgerufener Thrombose, Acta med. Scandinav. **70**:167, 1929.

38. (*a*) Zahn.[3] (*b*) Jones.[5] (*c*) Murray.[37h] (*d*) Moses, C.: An Evaluation of the Effect of Stasis in the Production of Experimental Thrombosis, Federation Proc. **4**:52, 1945; The Effect of Heparin and Dicoumarol on Thrombosis Induced in the Presence of Venous Stasis, Proc. Soc. Exper. Biol. & Med. **59**:25, 1945. (*e*) Hueper, W. C.: Expermental Studies in Cardiovascular Pathology: X. Effects

(Footnotes continued on next page)

entire wall or the intima or adventitia alone,[40] or the insertion through the wall into the lumen of foreign objects such as threads of fiber [41] or metal,[42] or metal, glass or collodion cannulas.[43] Platelet thrombi generally appeared within a short time. Apitz [10a] reported early stages of thrombus formation occurring as quickly as five minutes after the daubing of the outer wall of the vein of a rabbit with alcohol. Evidence of inflammation and even a coating of fibrin or other exudate were lacking at this stage.

The nature of thrombosis has been thought to be noninflammatory in the majority of cases in man studied by a number of observers.[44] Aschoff [8d] could find no well authenticated cases in the literature in

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of Repeated Intravenous Injections of Solutions of Digitonin on the Blood and the Internal Organs of Dogs and Rabbits, Arch. Path. **38**:326 (Nov.) 1944. (*f*) Solandt, D. Y., and Best, C. H.: Heparin and Coronary Thrombosis in Experimental Animals, Lancet **2**:130, 1938. (*g*) Kojima, S.: Experimentelle Untersuchungen über Veränderungen des Blutes durch aseptische Thrombenbildung, Arch. f. klin. Chir. **174**:216, 1933.

39. Zahn.[3] Eberth and Schimmelbusch.[8b] Fonio, A., and Vannotti, A.: Neuere Untersuchungen über die Entstehung der Thrombose, Schweiz. med. Wchnschr. **64**:1086, 1934.

40. Zahn.[3] Bizzozero.[4] Eberth and Schimmelbusch.[8b] Apitz.[10a] Solandt and Best.[38f] Dietrich, A.: Gefässwand und Thrombose, Verhandl. d. deutsch. Gesellsch. f. Kreislaufforsch., 1934, p. 48.

41. Mantegazza.[2] Zahn.[3] Bizzozero.[4] Osler.[6] Eberth and Schimmelbusch.[8b] Hayem.[37f] Zurhelle, E.: Experimentelle Untersuchungen über die Beziehungen der Infektion und der Fibringerinnung zur Thrombenbildung im strömenden Blut, Beitr. z. path. Anat. u. z. allg. Path. **47**:539, 1910.

42. Zahn.[3] Hayem.[37f]

43. (*a*) Best, Cowan and Maclean.[10b] (*b*) Dale and Jaques.[10d] (*c*) Rowntree, L. G., and Shionoya, T.: Studies in Experimental Extracorporeal Thrombosis: I. A Method for the Direct Observation of Extracorporeal Thrombus Formation, J. Exper. Med. **46**:7, 1927. (*d*) Bollman, J. L., and Preston, F. W.: The Effects of Experimental Administration of Dicoumarin: 3,3'-Methylene-Bis-(4-Hydroxycoumarin), J. A. M. A. **120**:1021 (Nov. 28) 1942. (*e*) Murray, G., and Janes, J. M.: Prevention of Acute Failure of Circulation Following Injury to Large Arteries: Experiments with Glass Cannulas Kept Patent by Administration of Heparin, Brit. M. J. **2**:6, 1940.

44. (*a*) Jorpes, J. E.: Heparin in the Treatment of Thrombosis: An Account of Its Chemistry, Physiology and Application in Medicine, ed. 2, London, Oxford University Press, 1946. (*b*) Hunter, W. C.; Krygier, J. J.; Kennedy, J. C., and Sneeden, V. D.: Etiology and Prevention of Thrombosis of the Deep Leg Veins: A Study of Four Hundred Cases, Surgery **17**:178, 1945. (*c*) Lenggenhager, K.: Ueber die Entstehung, Erkennung und Vermeidung der postoperativen Fernthrombose, Leipzig, Georg Thieme, 1941. (*d*) Murray, G., and MacKenzie, R.: Postoperative Thrombosis and Embolism, Am. J. Surg. **57**:414, 1942. (*e*) von Seemen, H., and Binswanger, H.: Ueber Allgemeinveränderungen, besonders des Blutes, nach chirurgischen Eingriffen und ihre Bedeutung für Entstehung und Bekämpfung der mittelbaren Operationsschädigungen, Deutsche Ztschr. f. Chir. **209**:157, 1928.

which thrombosis had really been brought about by changes in the endothelium; like many others he regarded physical factors (particularly sluggish blood flow and local eddy formation) as chief in importance.

Although histologic changes in endothelium may not be demonstrable, the possibility cannot be rejected that a physiochemical change is the basic local occurrence which cause platelets to adhere. As previously mentioned, platelet adhesion outside the body is determined by the presence of a wettable surface of glass or other material. The importance of wettability appears to lie chiefly in the fact that thrombin, which is probably necessary for initiating platelet adhesion and lysis as well as for blood clotting, can be produced from the interaction of a wettable surface and plasma even when the latter is practically platelet free.[45] Therefore, in order to explain thrombosis, it is necessary to postulate merely the development of wettability in the endothelium regardless of its normally maintained histologic appearance. The susceptibility of platelets to minute quantities of thrombin renders them a highly sensitive indicator of such endothelial change. The immunity of the intact, healthy subject to the spontaneous formation of platelet thrombi argues for the relative "nonwettability" of normal endothelium throughout the body. The concept of a "lack of adhesion" of the vascular lining was proposed by Freund [46] (1886) to explain the normal absence of clotting within living blood vessels as well as their failure to be stained by their contained blood. According to Clark,[47] the endothelium provides an extremely smooth lining to the whole of the cardiovascular system, minimizing friction in the flow of the blood and, in the smaller vessels, allowing the corpuscles to slip easily along its surface with no tendency to adhere. This character changes rapidly in response to any injurious stimulus (Clark and Clark [48]). If, for example, capillary endothelium is exposed to heat or to chemical irritants or receives mechanical injury, it becomes rather swollen and sticky, so that the corpuscles cling to its surface. In an extended study of the surface activity of a wide range of nonvital materials, including many which had water-repellent properties, Lampert [30i] concluded that

45. (*a*) Aynaud.[9c] (*b*) Lozner, E. L.; Taylor, F. H. L., and MacDonald, H.: Effect of Foreign Surfaces on Blood Coagulation, J. Physiol. **21**:241, 1942. (*c*) Nolf, cited by Lozner and others.[45b] (*d*) Ferguson, J. H.: A New Blood-Clotting Theory, Science **97**:319, 1943. (*e*) Lenggenhager, K.: Irrwege der Blutgerinnungsforschung, Klin. Wchnschr. **15**:1835, 1936.

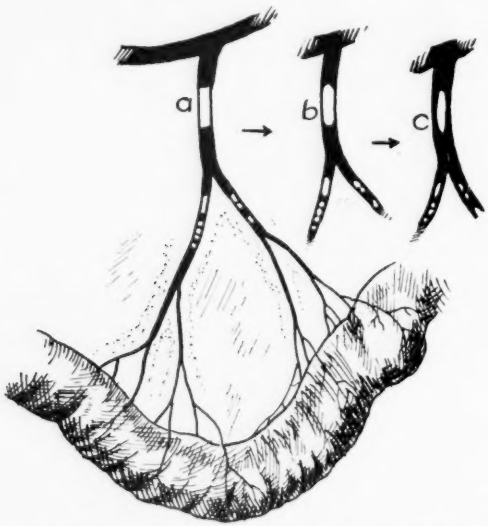
46. Freund, E.: Ein Beitrag zur Kenntniss der Blutgerinnung, Med. Jahrb. **1**:46, 1886.

47. Clark, W. E. Le Gros: The Tissues of the Body, ed. 2, Oxford, Clarendon Press, 1945, p. 168.

48. Clark, E. R., and Clark, E. L.: Observations on Changes in Blood Vascular Endothelium in the Living Animal, Am. J. Anat. **57**:385, 1935.

the rate of blood clotting and that of platelet attraction toward a particular type of surface were specifically related to its wettability. On the basis of his observations, he postulated a relation between endothelial wettability and the formation of white thrombi.

The development of wettability of endothelium can be readily demonstrated in the animal by a simple experiment.[49] Through a fine needle, a small bubble of air is introduced into one of the veins of a rabbit mesentery immediately after the animal has been killed and its abdominal cavity exposed. At first, the interface between blood and air appears as a very slightly concave meniscus. Within a short time the inter-



Development of endothelial wettability following cessation of circulation, as indicated by the formation of a concave meniscus between the blood and the air. *a*, Appearance of an air segment in a mesenteric vein shortly after the death of an experimental animal; *b*, eighteen minutes after death; *c*, forty-five minutes after death (sketch from actual experiment, showing how the initial slight concavity of the meniscus between blood and air is masked when in the direct line of vision but becomes clearly defined as the film of blood advances along the uncovered endothelium with increasing wettability).

face becomes more deeply concave, indicating thereby the progressive change from a relatively nonwettable endothelium to a highly wettable endothelium, as shown in the illustration. The experiment can be paralleled in nonvital materials by drawing blood into two narrow glass capillary tubes, one of which has been made nonwettable with paraffin or silicone; in the treated tube the upper end of the column

49. Moolten, S. E., and Vroman, L.: Unpublished data, 1948.

of blood is seen to be a flat meniscus, in contrast to the concave meniscus formed by blood in ordinary glass. In addition, a striking lack of friction in the inflow and outflow of blood can be demonstrated in the nonwettable tube when compared with the other.

The relative nonwettability of healthy endothelium, which is important in maintaining a frictionless inner lining of blood vessels as well as a fluid condition of the blood itself, may therefore be postulated as an actively vital property of endothelial cells in general and as probably dependent, as such, on the adequacy of their nutrition and organization. Accordingly, factors which affect the nutrition of the inner layers of blood vessels, impairing their vitality and causing endothelium to lose its physiologic nonwettability, may rightfully be regarded as the basic local determinants of thrombus formation. Chief among these factors is arteriosclerosis (more particularly, atheroma) which is rarely lacking when thrombosis appears in a coronary or cerebral artery or in one in a limb.[50] Damage to the endothelium covering an atheromatous plaque, either calcified or distended with old or recent hemorrhage, is partly the result of mechanical injury and partly due to loss of the normal intimal cushion which ordinarily protects and nourishes the lining cells. In the lower extremities, calcification of the media may play a part in causing intimal damage and thrombosis, possibly through simple mechanical interference with nutrition of the inner layers.[51] A similar mechanism may underlie thrombosis following prolonged external compression of an artery by a cervical rib,[52] by the use of a crutch [53] or by the habitual crossing of the legs over the knees.[54] Prolonged vasospasm, curtailing the flow of nutrients from adventitial vessels through the tightly contracted media, appears to be a decisive contributing factor in the progress of organic changes in the intima in peripheral vascular disease,

50. (*a*) Allen, E. V.; Barker, N. W., and Hines, E. A., Jr.: Peripheral Vascular Diseases, Philadelphia, W. B. Saunders Company, 1946. (*b*) Paterson, J. C.: Capillary Rupture with Intimal Hemorrhage as a Causative Factor in Coronary Thrombosis, Arch. Path. **25**:474 (April) 1938. (*c*) Horn, H., and Finkelstein, L. E.: Arteriosclerosis of the Coronary Arteries and the Mechanism of Their Occlusion, Am. Heart J. **19**:655, 1940. (*d*) Wright, I. S., and Foley, W. T.: Use of Anticoagulants in the Treatment of Heart Disease, with Special Reference to Coronary Thrombosis, Rheumatic Heart Disease with Thromboembolic Complications and Subacute Bacterial Endocarditis, Am. J. Med. **3**:718, 1947. (*e*) Graef, I., cited by Wright and Foley.[50d] (*f*) Aring, C. D., and Merritt, H. H.: Differential Diagnosis Between Cerebral Hemorrhage and Cerebral Thrombosis: A Clinical and Pathologic Study of Two Hundred and Forty-Five Cases, Arch. Int. Med. **56**:435 (Sept.) 1935.

51. Personal observation.

52. Allen, Barker and Hines.[50a]

53. Platt, H.: Occlusion of the Axillary Artery Due to Pressure by a Crutch: Report of Two Cases, Arch. Surg. **20**:314 (Feb.) 1930.

54. London, I. M.: Personal communication to the authors.

such as thromboangiitis obliterans and arteriosclerosis,[55] as well as in such definitive vasospastic disorders as Raynaud's disease [56] and ergotism,[55c] and may well be the critical factor in precipitating thrombosis in all these conditions. Similar mechanisms may be involved in the thromboses of frostbite.[57] Pressure on the deep veins of the legs during prolonged recumbency on a firm mattress has been charged with principal responsibility for phlebothrombosis following operations.[58]

The etiologic principles concerned in arterial and venous thrombosis can be extended to explain the formation of large mural ventricular thrombi in cases of myocardial infarction.[59] These constitute one of the chief causes of serious or fatal issue in the wake of the acute attack. Mural thrombi of the ventricles may result from various other inflammatory and degenerative lesions of heart muscle, such as Fiedler's myocarditis [60] and idiopathic cardiac hypertrophy of adults.[61] Similar factors are concerned also in the formation of mural thrombi of the atriums and atrial appendages in which conditions of flow are such

55. (*a*) Bernheim, A. R., and London, I. M.: Arteriosclerosis and Thrombo-Angiitis Obliterans: Report of Cases and Treatment, J. A. M. A. **108**:2102 (June 19) 1937. (*b*) Hueper, W. C.: Arteriosclerosis, Arch. Path. **38**:245 (Oct.) 1944; (*c*) p. 278.

56. Lewis, T., and Pickering, G. W.: Observations on Maladies in Which Blood Supply to Digits Ceases Intermittently or Permanently and on Bilateral Gangrene of Digits: Observations Relevant to So-Called "Raynaud's Disease," Clin. Sc. **1**:327, 1934.

57. Lange, K., and Boyd, L. J.: Use of Fluorescein Method in Establishment of Diagnosis and Prognosis of Peripheral Vascular Diseases, Arch. Int. Med. **74**:175 (Sept.) 1944; Science **102**:151, 1945.

58. (*a*) Rössle, R.: Ueber die Bedeutung und die Entstehung der Wadenvenenthrombosen, Virchows Arch. f. path. Anat. **300**:180, 1937. (*b*) Frykholm, R.: The Pathogenesis and Mechanical Prophylaxis of Venous Thrombosis, Surg., Gynec. & Obst. **71**:307, 1940.

59. Welch.[8c] Solandt, D. Y., Nassim, R., and Best, C. H.: Production and Prevention of Cardiac Mural Thrombosis in Dogs, Lancet **2**:592, 1939. Nay, R. M., and Barnes, A. R.: Incidence of Embolic or Thrombotic Processes During Immediate Convalescence from Acute Myocardial Infarction, Am. Heart J. **30**:65, 1945. Hellerstein, H. K., and Martin, J. W.: Incidence of Thrombo-Embolic Lesions Accompanying Myocardial Infarction, ibid. **33**:443, 1947.

60. Fiedler, A.: Ueber akute interstitielle Myokarditis, Centralbl. f. inn. Med. **21**:212, 1900. Scott, R. W., and Saphir, O.: Acute Isolated Myocarditis, Am. Heart J. **5**:129, 1929. de la Chapelle, C. E., and Graef, I.: Acute Isolated Myocarditis, with Report of Case, Arch. Int. Med., **47**:942 (June) 1931.

61. Levy, R. L., and Rousselot, L. M.: Cardiac Hypertrophy of Unknown Etiology in Young Adults, Am. Heart J. **9**:178, 1933. Dock, W.: Marked Cardiac Hypertrophy and Mural Thrombosis in the Ventricles in Beriberi Heart, Tr. A. Am. Physicians **55**:61, 1940. Smith, J. J., and Furth, J.: Fibrosis of the Endocardium and the Myocardium with Mural Thrombosis: Notes on Its Relation to Isolated (Fiedler's) Myocarditis and to Beriberi Heart, Arch. Int. Med. **71**:602 (May) 1943.

that massive red thrombi may result; this is particularly true in severe mitral stenosis, in which the left atrium may become completely occluded.[8c]

Nonbacterial thromboendocarditis of varying types[62] is probably determined by the same principles. When the vegetations occur on previously normal valvular endocardium, the wettability which favors such platelet deposition may be part of the endothelial component of diffuse mesenchymal disease or the result of advanced debility and cachexia.

The vegetations which are formed on the heart valves in bacterial endocarditis are composed principally of masses of platelets agglutinated about bacterial colonies.[63] The platelet component, because of its bulk, constitutes a double hazard, increasing the size of emboli and shielding the micro-organisms from the action of antibacterial agents in the circulating blood. It is conceivable that a preparatory deposit of sticky platelets, accumulating on areas of wettable endocardium such as may develop on preexisting lesions of rheumatic endocarditis or congenital deformities of the valves or chambers, supplies the initial anchorage of such micro-organisms carried thence in the course of transient bacteremia.

The intravascular action of fat solvents and of detergent substances is logically explained in terms of their effect on the endothelium. Small amounts of dilute ethyl alcohol can be shown to increase endothelial wettability rapidly at the site of injection in a mesenteric vein prepared with an air bubble according to the technic described previously.[49] The intravenous administration of ether has long been known to cause extensive thrombosis, beginning at the site of administration (Aschoff,[30j] Lampert[30l]). Saponins, such as digitonin, injected intravenously may produce thrombi at the site of injection as well as in distant vessels.[38e] The presence of saponins in crude digitalis preparations may be responsible, according to Hueper,[38e] (possibly through their effects on endothelial wettability) for the increased incidence of thrombi after digitalis therapy reported by de Takats.[64] It is unnecessary to invoke the hypothesis that such thrombi result from the thromboplastic action of digitalis, a hypothesis which has been disputed by a number of observers.[65]

62. Gross, L., and Friedberg, C. K.: Nonbacterial Thrombotic Endocarditis: Classification and General Description, Arch. Int. Med. **58**:620 (Oct.) 1936.

63. Osler.[6] Welch.[8c] Personal observation.

64. de Takats, G., Trump, R. A., and Gilbert, N. C.: The Effect of Digitalis on the Clotting Mechanism, J. A. M. A. **125**:840 (July 22) 1944.

65. (*a*) Moses, C.: The Effect of Digitalis, Epinephrine, and Surgery on the Response to Heparin, J. Lab. & Clin. Med. **30**:603, 1945. (*b*) Sokoloff, L.; Ferrer, M. I., and DeGraff, A. C.: The Effect of Digitalization on the Coagulation Time of the Blood in Man, Federation Proc. **4**:136, 1945.

The foregoing description of the genesis of thrombosis may be epitomized in the following manner:

1. The alteration of endothelial lining, even when not demonstrable histologically, may render it more wettable and initiate thereby the local production of thrombin.

2. Platelets swept into contact with such altered endothelium adhere to it and are in turn made further agglutinable by the lytic action of locally formed thrombin, thereby entrapping other platelets in large numbers. As their lysis proceeds to completion the agglutinated platelets liberate accelerator substances which intensify the local production of thrombin. If the blood flow is rapid, much of the deposit of thrombin and platelets is swept away. If the current is relatively sluggish, platelets are deposited in rapidly mounting number until the lumen is totally occluded by white thrombus.

3. Continued elaboration of thrombin under the accelerating influence of platelet lysis en masse in the newly formed white thrombus quickly results in clotting of the entire column of stagnant blood above and below it to form a red thrombus. In a vein, the red thrombus, attached at first only to the sticky platelets comprising the white thrombus, may become dislodged as an embolus, especially after its retraction. Endothelial wettability may facilitate the latter process, as indicated later in this report.

QUALITATIVE AND QUANTITATIVE VARIATIONS IN BLOOD PLATELETS

It is now generally appreciated that the varying susceptibility of individual subjects to thrombosis or to hemorrhage may be correlated, to a large extent, with differences in the characteristics of the blood platelets. Numerical differences are apparently overshadowed by qualitative differences, which can be demonstrated morphologically [66] or by technics for measuring the rate of platelet lysis [67] or agglutination [68]

66. (*a*) Tocantins.[9g] (*b*) Rosenthal.[9i] (*c*) Jürgens.[11d] (*d*) Frank.[12e] (*e*) Jürgens and Naumann.[13g] (*f*) Jürgens, R., and Graupner, H.: Darstellung eines Entwicklungssystems der Thrombocyten: Zugleich ein Beitrag über das "Blutplättchenbild" der Blutkrankheiten, Folia haemat. **57**:263, 1937. (*g*) Arneth, J.: Ueber das qualitative (im engeren Sinne biologische) Verhalten der Blutplättchen bei der Perniciosa (qualitatives Thrombocytenblutbild), ibid. **57**:1, 1937. (*h*) Ueber das qualitative Verhalten der Thrombocyten und Leukocyten bei der Hämophilie und bei der essentiellen Thrombopenie, ibid. **57**:166, 1937. (*i*) Olef, I.: The Differential Platelet Count: Its Clinical Significance, Arch. Int. Med. **57**:1136 (June) 1936.

67. (*a*) Baar and Székely.[13b] (*b*) Lee, P., and Erickson, B. N.: Platelet Studies in Normal Men and Women (Menstruating and Nonmenstruating) and Subjects with Bleeding Disorders, J. Lab. & Clin. Med. **24**:821, 1939. (*c*) Olef, I.: Rate of Disintegration of Platelets, ibid. **22**:128, 1936; cited by Lee and

in vitro. Platelets which appear defective morphologically or which lack the capacity of becoming readily agglutinated tend to be inefficient in arresting hemorrhage despite their presence in normal numbers.[69] Such platelets are characteristic of purpura hemorrhagica associated with splenic hypertrophy ("hypersplenism").[70] After splenectomy and coincident with cessation of the bleeding tendency they may no longer be observed, even in cases in which the total platelet count returns to the previous low level.[71] Conversely, the increased capacity of platelets to agglutinate or adhere often coincides with an increased tendency to thrombosis and to shortened bleeding time. Such an increase in platelet agglutinability and adhesiveness has been noted with fair

Erickson.[67b] (*d*) Muhrer, M.; Bogart, R., and Hogan, A.: Estimation of Platelet Fragility, Am. J. Physiol. **141**:449, 1944. (*e*) Tocantins, L. M.; Technical Methods for the Study for the Blood Platelets: A Critical Review with Bibliography, Arch. Path. **23**:850 (June) 1937.

68. (*a*) Jürgens and Naumann.[13g] (*b*) von Seemen and Binswanger.[44e] (*c*) Ollgaard, E.: On the Agglutination of the Blood Platelets Under Normal and Pathological Conditions, Acta med. Scandinav. **115**:1, 1943. (*d*) Copley, A. L., and Robb, T. P.: Studies on Platelets: III. The Effect of Heparin in Vivo on the Platelet Count in Mice and Dogs, Am. J. Clin. Path. **12**:563, 1942. (*e*) Copley, A. L.: Embolization of Platelet Agglutination Thrombi in the Hamster's Pouch Produced by Heparin, Federation Proc. **7**:22, 1948. (*f*) Copley, A. L., and Houlihan, R. B.: On the Mechanism of Platelet Agglutination, ibid. **4**:173, 1945.

69. (*a*) Jürgens.[11d] (*b*) Frank.[12e] (*c*) Footnote 13 *c*, *g* and *i*. (*d*) Brill, N. E., and Rosenthal, N.: Treatment by Splenectomy of Essential Thrombocytopenia (Purpura Hemorrhagica), Arch. Int. Med. **32**:939 (Dec.) 1923. (*e*) Rosenthal, N.: Hemorrhagic Diatheses: Thrombocytopenia, Thrombasthenia, Capillary (Hemorrhagic) Toxicosis, Hemophilia and Thrombocythemia, in Downey, H.: Handbook of Hematology, New York, Paul B. Hoeber, Inc., 1938, vol. 1, sect. 8, p. 501. (*f*) Uotila, U.: On Hemorrhagic Thrombocythemia, Acta med. Scandinav. **95**:136, 1938. (*g*) Epstein, E., and Goedel, A.: Hämorrhagische Thrombocythämie bei vasculärer Schrumpfmilz, Virchows Arch. f. path. Anat. **292**:233, 1934. (*h*) Reid, J.: Haemorrhagic Thrombocythaemia, Lancet **2**:584, 1940. (*i*) Frank, E., Die hämorrhagischen Diathesen, in Schittenhelm, A.: Enzyklopädie der inneren Medizin (special part 10): Handbuch der Krankheiten des Blutes und der blutbildenden Organe, Berlin, Julius Springer, 1925, vol. 2, p. 289. (*j*) Bernard, J., and Soulier, J. P.: Investigation of a New Variety of Congenital Hemorrhagic Thrombocytic Dystrophy, read before the International Society of Hematology, Buffalo, N. Y., Aug. 23, 1948.

70. Jürgens.[11d] Baar.[13c] Jürgens and Naumann.[13g] Brill and Rosenthal.[69d]

71. (*a*) Jürgens.[11d] (*b*) Jürgens and Graupner.[66f] (*c*) Rosenthal, N., The Course and Treatment of Thrombopenic Purpura, J. A. M. A. **112**:101 (Jan. 14) 1939. (*d*) Leschke, E., and Wittkower, E.: Die Werlhofsche Blutfleckenkrankheit (thrombopenische Purpura): Ein Beitrag zur Pathologie der Blutplättchen und Capillaren und zur Pathogenese der hämorrhagischen Diathese, Ztschr. f. klin. Med. **102**:649, 1925-1926.

regularity after operations,[72] after childbirth [13d] and in convalescence from infectious diseases,[30i] especially typhoid.[73]

THROMBOCYTOSIN AND THROMBOCYTOPEN

The experimental data of Aynaud [9c] (1909) and others [74] indicate that platelet agglutination can readily be brought about in vitro and in vivo by the addition to blood of peptones, various colloids, fatty emulsions, saponin, bile salts and tissue juices expressed from muscle, from fascia and, especially, from adipose tissue.[9c] It is probable that autolyzing tissues, such as those of large cancers, bring about similar effects in vivo through activation or liberation of proteolytic and lipolytic enzymes.

In 1944, one of us (S. E. M.)[75] undertook to investigate various organic factors which influence the number of blood platelets in circulation. A lipid substance was discovered which, when injected into normal rabbits or fed to human subjects with thrombopenia, proved to be highly effective in increasing the rate of production of blood platelets. This factor, termed "thrombocytosin," was found in abundance in subcutaneous fat, in egg yolk and in lymph nodes. It was virtually absent in brain tissue, liver, bone marrow and perirenal fat. It was abundant in the spleen, although normally in smaller quantity than its physiologic antagonist, "thrombocytopen." The possibility that thrombocytosin is inactivated in the spleen was suggested by the observation of large amounts of thrombocytosin in the urine of a splenectomized subject in contrast to the much smaller amount in normal persons.

Subsequent studies of thrombocytosin [76] disclosed the important fact that it also increases the adhesiveness of platelets in vitro and in the living animal. In therapeutic trials, it was helpful in several cases of abnormal bleeding when given orally or by intramuscular injection. Parallel with the reduced tendency to bleed, a rise occurred in the platelet count and in the platelet adhesiveness, which was measured

72. (*a*) Jürgens.[11d] (*b*) Wright.[13d] (*c*) Starlinger and Sametnik.[29] (*d*) von Seemen and Binswanger.[44e] (*e*) Olef.[66i] (*f*) Øllgaard.[68c] (*g*) Mackay, W.: The Blood Platelet: Its Clinical Significance, Quart. J. Med. **24**:285, 1931.

73. Hartmann, E.: Ueber das Verhalten der Blutplättchen beim Typhus abdominalis, Deutsches Arch. f. klin. Med. **158**:1, 1927.

74. (*a*) Tocantins.[9g] (*b*) Quick, A. J.; Ota, R. K., and Baronofsky, I. D.: On the Thrombopenia of Anaphylactic and Peptone Shock, Am. J. Physiol. **145**:273, 1946.

75. Moolten, S. E.: Studies on Extractable Factors in the Spleen and Other Organic Sources Which Influence the Blood Platelet Count, J. Mt. Sinai Hosp. **12**:866, 1945.

76. Moolten, S. E., and Vroman, L. Unpublished data, 1947-1948.

by the glass wool filter method, as described in the section on that technic. In 1 case of thrombopenic purpura, a single dose of 50 mg. given parenterally reduced the bleeding time (Ivy method) from more than thirty minutes to six and three-quarters minutes; in another case it was reduced from over thirty-five minutes to four and one-half minutes. In a third case, that of a girl of 15, in which purpura was manifested chiefly as severe and protracted menorrhagia, thrombocytosin given prior to the onset of menses resulted in a normal flow lasting four to five days. It also alleviated, at least temporarily, the gingival bleeding of a patient with monocytic leukemia.

The existence of thrombocytosin was foreshadowed in the studies of Kugelmass,[77] who showed that a diet high in fat and protein in cases of thrombopenic purpura causes the blood platelet count to rise from low to normal, with the simultaneous disappearance of the hemorrhagic tendency. Similar findings were reported by Schiff and Hirschberger,[78] using egg yolk or sesame oil. They predicated the occurrence in these materials of a specific thrombocytosis-producing factor, the "fat-soluble T factor," although they did not isolate it. Acting on Kugelmass' evidence, Bancroft[79] employed a low fat, low protein diet in the prophylaxis of thromboembolism in surgical patients.

Among the many causes of increased platelet count, trauma to tissues (conspicuously laparotomy and fracture of the thigh), has been regarded as particularly significant.[80] The peak of postoperative thrombocytosis is generally recorded as being reached during the second week and has been stated to coincide approximately with the time of the greatest incidence of thromboembolism.[81] The increase in plate-

77. Kugelmass, I. N.: Clinical Control of Chronic Hemorrhagic States in Childhood, J. A. M. A. (Jan. 20, 1934); "Bleeding" and "Clotting" Diets, M. Clin. North America **19**:989, 1935.

78. Schiff, E., and Hirschberger, C.: Thrombocytosis Produced by a Hitherto Unknown Substance—the "Fat-Soluble T Factor," Am. J. Dis. Child. **53**:32 (Jan., pt. 1) 1937; Ueber den T-Faktor, Jahrb. f. Kinderh. **150**:247, 1937.

79. Bancroft, F. W.; Stanley-Brown, M., and Chargaff, E.: Postoperative Thrombosis and Embolism, Ann. Surg. **106**:868, 1937.

80. (*a*) Dawbarn, R. Y.; Earlam, F., and Evans, W. H.: The Relation of the Blood Platelets to Thrombosis After Operation and Parturition, J. Path. & Bact. **31**:833, 1928. (*b*) Hueck and Galloway, cited by Tocantins.[9g] (*c*) König, W.: Experimentelle Untersuchungen über die Entstehung der Thrombose: Ein Beitrag sur Lehre von den Blutplättchen, Arch. f. klin. Chir. **171**:447, 1932. (*d*) Adams, E.: Postoperative Thrombocytosis, Arch. Int. Med. **73**:329 (April) 1944. (*e*) Wright, H. P.: Changes in Numbers of Circulating Blood Platelets Following Experimental Traumata, J. Obst. & Gynaec. Brit. Emp. **52**:253, 1945. (*f*) Evans, W. I., and Fowler, W. M.: Effect of Splenectomy and Other Operative Procedures on Platelets as Determined Volumetrically, Proc. Soc. Exper. Biol. & Med. **32**:512, 1934.

81. Dawbarn, Earlam and Evans.[80a] Adams.[80d]

lets has been atributed to specific products of the breakdown of tissue which stimulate the activity of megakaryocytes, for example, products of nuclear breakdown [80c] or, as previously suggested by one of us (S. E. M.),[75] thrombocytosin mobilized from traumatized fat cells. Thrombocytosis of similar or much greater degree has been provoked by a variety of factors having in common a solvent or lytic action on adipose tissue, e. g., irritation of the skin by ultraviolet light, iodine or generalized dermatoses [82] and injections of turpentine,[83] saponin,[83] pyridine,[24] pyrodine (acetyl phenylhydrazine) [84] or lecithin.[85]

The sustained thrombocytosis, often reaching levels well above 1,000,000 platelets, which is encountered regularly after splenectomy is regarded by many as a release phenomenon occasioned by removal of a normal suppressive influence [86] rather than by a primary stimulation of the marrow.

Thrombocytopen, a lipid substance found in the normal spleen,[75] is greatly increased in amount in the spleen of idiopathic purpura hemorrhagica,[75] from which it was originally extracted in crude form by Troland and Lee.[87] On the other hand, in thrombopenia caused by bone marrow insufficiency, such as aplastic anemia or leukemia, splenic assay for thrombocytopen may show much less than the normal amount, particularly when the splenic pulp has became partly fibrous or has been replaced by leukemic cells.[75] Although separated with difficulty from thrombocytosin because of many chemical and physical similarities, its biologic effects are almost completely opposite. As

82. (*a*) Steiner, P. E., and Gunn, F. D.: The Response of Blood Platelets to External Stimuli: Ultraviolet Light, Iodine and Coal Tar, Arch. Path. **11**:241 (Feb.) 1931. (*b*) Gunn, F. D.: Reactions of the Bone Marrow in Experimentally Induced Thrombocytosis, ibid. **12**:153 (Aug.) 1931.

83. Bunting, C. H.: Blood-Platelet and Megalokaryocyte Reactions in the Rabbit, J. Exper. Med. **11**:541, 1909.

84. Mariconda, G.: Osservazioni intorno alla origine istiocitaria delle piastrine del sangue, Arch. di fisiol. **32**:387, 1933. Ferrata and Rinaldo, cited by Gunn.[82b] Frey, Jürgens and Bach, cited by Olef.[66l]

85. Ma, cited by Tocantins.[9g]

86. (*a*) Brill and Rosenthal.[69d] (*b*) Frank,[69l] (*c*) Lauda, E.: Die normale und pathologische Physiologie der Milz, Berlin, Urban & Schwarzenberg, 1933. (*d*) Schousboe, J.: Two Cases of Splenic Control of the Cell Emission from the Bone Marrow, Acta med. Scandinav. **103**:123, 1940. (*e*) Singer, K.; Miller, E. B., and Dameshek, W.: Hematologic Changes Following Splenectomy in Man, with Particular Reference to Target Cells, Hemolytic Index and Lysolecithin, Am. J. M. Sc. **202**:171, 1941.

87. Troland, C., and Lee, F.: A Preliminary Report on a Platelet-Reducing Substance in the Spleen of Thrombocytopenic Purpura, Bull. Johns Hopkins Hosp. **62**:85, 1938; Thrombocytopen: A Substance in the Extract from the Spleen of Patients with Idiopathic Thrombocytopenic Purpura That Reduces the Number of Blood Platelets, J. A. M. A. **111**:221 (July 16) 1938.

will be indicated later in this paper, thrombocytopen lowers the platelet count and platelet adhesiveness in the living subject and reduces platelet adhesiveness in vitro. After its administration in man, the proportion of large platelets is increased.[76] Although both thrombocytopen and thrombocytosin appear in the urine of normal persons, thrombocytopen is undetectable after splenectomy.[75]

Thrombocytosin and thrombocytopen are, in effect, physiologic antagonists competing for a common substrate, the blood platelet and its parent megakaryocyte. For reasons which will be developed elsewhere in this paper, it appears reasonable to regard the unbalanced activity of either factor as an important element in the pathogenesis of either thromboembolic disease or idiopathic purpura.

OTHER FACTORS IN THROMBUS FORMATION

Emphasis on the importance of sluggish blood flow in thrombus formation received its impetus principally from the work of Virchow nearly a century ago and has become part of all orthodox teaching. The physical structure of white thrombi is believed to be determined largely by local mechanical conditions which govern the manner and rate of platelet deposition on endothelial surfaces so altered that platelet adhesion can occur. Von Recklinghausen [88] was among the first to appreciate the part played by local eddy currents in the blood stream, and Eberth and Schimmelbusch [8b] soon offered experimental confirmation. The effect was described by Aschoff [8d] as not unlike the silting up of sand along a breakwater or jetty in a slowly flowing river, an effect particularly noticeable on the outer surface of venous valves or in the bay of an abrupt widening of the lumen of a vessel just beyond a point of narrowing. The role of platelet "stickiness" as a necessary factor in this sandbank effect was studied experimentally by Lenggenhager,[44c] employing thrombin-coated kaolin powder.

The significance of prolonged recumbency, on which a large body of current theory of thrombosis is based, has recently undergone reevaluation by Powers,[89] Blodgett and Beattie [90] and Allen, Linton and Donaldson.[91] According to their clinical data the over-all incidence of postoperative thrombosis is not diminished by early postoperative

88. von Recklinghausen, cited by Eberth and Schimmelbusch[8b] and Welch.[8c]

89. Powers, J. H.: Postoperative Thromboembolism: Some Remarks on the Influence of Early Ambulation, Am. J. Med. **3**:224, 1947.

90. Blodgett, J. B., and Beattie, E. J.: Early Postoperative Rising: A Statistical Study of Hospital Complications, Surg., Gynec. & Obst. **82**:485, 1946.

91. (*a*) Allen, A. W.; Linton, R. R., and Donaldson, G. A.: Venous Thrombosis and Pulmonary Embolism, J. A. M. A. **133**:1268 (April 26) 1947. (*b*) Chapman, E. M., and Linton, R. R.: Mode of Production of Pulmonary Emboli, ibid. **129**:196 (Sept. 15) 1945.

rising but, if anything, may be increased; yet, the danger of fatal pulmonary embolism is appreciably lessened. The apparent paradox can easily be explained by the twofold origin of thrombi: Red thrombi, which constitute the principal element in embolism, can develop only in the presence of a complete standstill of circulation, such as follows venous occlusion by white thrombi, and owe their dangerous quality to the size they achieve through propagation in a quiet limb. White thrombi, on the other hand, can form only while circulation persists, however sluggishly, in order to provide a constant supply of fresh platelets for their continued growth. Evidences already given indicate that the white thrombus, to which basic guilt attaches in thrombotic disease, owes its size and rapidity of formation (1) to the number of sticky platelets available, (2) to endothelial wettability and (3) to conditions of flow which favor platelet agglutination to the vessel wall and to one another. Even rapid flow, as in the cardiac chambers, the aorta or the large arteries, does not necessarily prevent formation of white thrombus when other favoring influences exist.[92]

Rössle,[58a] Frykholm[88b] and others[93] have drawn attention to the predominant origin of deep venous thrombi in the muscular twigs of the deep veins of the thighs and legs. In the opinion of the first two writers, a type of decubitus injury is caused in these vessels by the pressure of a firm mattress against the calf muscles or by that of the adductor muscles of the thighs against each other. Other factors may be the angulation of penetrating veins by side to side passive movements of calf muscles during dorsal recumbency and the activity of products of muscular degeneration resulting from prolonged inactivity and compression.[58a] It remains to be tested whether or not thrombocytosin is also released by pressure atrophy of subcutaneous fat tissue in prolonged recumbency. Another factor deserving attention, particularly in relation to endothelial wettability, is the phenomenon of "sludge" formation.[94]

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92. Osler.[6] Best, Cowan and Maclean.[10b] Rowntree and Shionoya.[42a] Murray and Janes.[43e] Gross and Friedberg.[62] De Santo, D. A.: Operation and Trauma as a Cause of Coronary and Cerebral Thrombosis, Am. J. Surg. **26**:35, 1934.

93. (*a*) Hunter and others.[44b] (*b*) Homans, J.: Venous Thrombosis in the Lower Limbs: Its Relationship to Pulmonary Embolism, Am. J. Surg. **38**:316, 1937. (*c*) Bauer, G.: Heparin Therapy in Acute Deep Venous Thrombosis, J. A. M. A. **131**:196 (May 18) 1946. (*d*) de Takats, G., and Fowler, E. F.: The Problem of Thrombo-Embolism, Surgery **17**:153, 1945. (*e*) Ochsner, A.: Venous Thrombosis, J. A. M. A. **132**:827 (Dec. 7) 1946. (*f*) Neumann, R.: Ursprungszentren und Entwicklungsformen der Beinthrombose, Virchows Arch. f. path. Anat. **301**:708, 1938.

94. Knisely, M. H.; Bloch, E. H.; Eliot, T. S., and Warner, L.: Sludged Blood, Science **106**:431, 1947.

PROPAGATION OF THROMBI

The formation of a massive thrombus by propagation from small thrombi within tributary twigs of the main venous channels of the leg or thigh has been explained[8c, d] as the result of segmental formation of white thrombi wherever a vein filled with red thrombus joins another vein which is patent. In the latter vessel, freely flowing blood conveys fresh platelets past the projecting "tail" of red thrombus, which, being a site of active clotting, attracts and agglutinates platelets en masse. When the succeeding vessel has, in turn, become occluded by white thrombus, the thrombus again acts as a nucleus about which clotting occurs to form a new red thrombus up to the level of the next juncture, and so on. It is commonly held today that phlebothrombosis of the lower extremities usually begins in the deep vessels of the calf and tends to propagate toward the heart. Thrombosis of the femoral vein, from which massive emboli spring, is thought to be rarely primary, contrary to older views including those of Aschoff,[8d] but to represent an extension of smaller thrombi beginning in the legs or feet.[95]

PRODUCTION OF EMBOLISM

Apparently little affinity exists between fibrin and the normal endothelial lining; hence long intravascular clots may easily be pulled out from veins.[9k] It is obviously at this stage of development of the red thrombus that the risk of embolism is greatest. The duration of this stage, however, is generally no more than twenty-four to forty-eight hours.[96] Thereafter, the wall of the occluded vein becomes the seat of an aseptic inflammatory process which results in the fixation of red thrombus by organization, accompanied with tenderness and other local signs of inflammation.

Little is known of the possible determining factors in embolism. Mechanical influences, such as active movement of the limbs on getting out of bed, account in many instances for dislodgment of emboli. Straining movements in bed, which temporarily raise venous pressure and thus provoke a tidal recoil of venous blood, are held accountable by Chapman and Linton[91b] for "bedpan deaths" from pulmonary embolism in bedridden patients. Nevertheless, the small proportion of emboli which actually arise in cases of venous thrombosis[50a] compels one to search for some additional causative factor or factors. Hirschboeck and Coffey[97] drew attention to the role of clot retraction

95. Rössle.[88a] Footnote 93.

96. Allen, Barker and Hines.[50a] Bauer.[93c]

97. (*a*) Hirschboeck, A. S., and Coffey, W. L., Jr.: Clot Retraction Time in Thrombophlebitis and Pulmonary Embolism, Am. J. M. Sc. **205**:727, 1943. (*b*) Hirschboeck, J. S.: Delayed Blood Coagulation and Absence of Clot Retraction in Collodion Lined Vessels, Proc. Soc. Exper. Biol. & Med. **45**:122, 1940.

in the formation of emboli and reported pronounced shortening of clot retraction time in a high proportion of cases of pulmonary embolism. Formation of a protective blanket of serum about a red thrombus must obviously interfere with its attachment to the wall of the vein and facilitate its mobilization as an embolus. At least two factors are concerned in clot retraction ("syneresis"): (1) the presence of blood platelets and (2) the nature of the surface of contact. The optimal retraction of clot in glass tubes requires an adequate number of intact qualitatively normal platelets (Tocantins[98]). Postoperative thrombocytosis may accelerate clot retraction.[99] Thrombin formation, especially the accelerated formation resulting from the catalytic activity of hyperadhesive platelets, may play a role, a possibility suggested by the discovery that a suspension of fine carbon particles (norit®) coated with thrombin can induce normal clot retraction in deplateletized plasma.[76] On the other hand, clot retraction is inhibited by the contact of clotted blood with collodion surfaces (Hirschboeck[97b]). In Lampert's opinion,[301] the most important factor in embolism is the quickening influence on clot retraction of pronounced wettability in the vessel wall. How endothelial wettability aids clot retraction is not altogether clear. Personal observations[76] of clotting blood on glass slides and on slides coated with water-repellent plastics suggest that the deciding element is rapid lysis of blood platelets in contact with a wettable surface, whereby fibrin filaments lose their means of attachment. In that event the role of endothelial wettability becomes doubly important, initiating platelet deposition as the mechanism of the white thrombus and favoring retraction of the red thrombus to increase the threat of embolism.

CHANGES IN THE CIRCULATING BLOOD SECONDARY TO THROMBUS FORMATION

Distinct lowering of the prothrombin level, measured by the one stage method (Quick), was observed shortly after thrombosis in some of our cases, but the level was not tested by the two stage method. It is possible that losses of prothrombin under these circumstances are quickly replaced; in contrast, a marked permanent loss of prothrombin (about 85 per cent, according to Quick[85b]) occurs during clotting in the test tube.

98. Tocantins, L. M.: Platelets and the Spontaneous Syneresis of Blood Clots, Am. J. Physiol. **110**:278, 1934; Platelets and the Structure and Physical Properties of Blood Clots, ibid. **114**:709, 1936.

99. Lampert.[301] Hirschboeck and Coffey.[97a]

Increased clotting activity has been reported by a number of observers [100] in cases of thrombosis and has been adduced as evidence that the underlying cause of thrombosis is an increase in circulating thromboplastin and other clotting factors.[101] Ogura and his associates,[100g] however, reported data from cases of coronary thrombosis which indicate that increased clotting activity (measured by a modified heparin tolerance test in vitro) follows rather than precedes coronary thrombosis and may therefore be the result of damage to myocardial tissue. Shafiroff [102] demonstrated that clotting activity in venous blood obtained from an extremity already affected by thrombosis was greater than that obtained from the opposite extremity.

Our own observations in patients with thrombosis (to be described later in the paper) likewise suggest that increased clotting activity, measured by prothrombin time, clot retraction time [97a] and heparin tolerance in vitro,[100h] is not a primary cause of thrombosis but, rather, the secondary manifestation of the presence of a white thrombus. As already stated, such a thrombus is composed principally of agglutinated platelets which undergo lysis and thereby accelerate the production of thrombin from precursor elements. Quick [85b] stated the belief that the normal platelet lysin is thrombin itself, evolved initially in minute amounts and evoking, thence, a chain reaction in which the

100. (*a*) Bancroft, Stanley-Brown and Chargaff.[79] (*b*) Nygaard, K. K., and Brown, G. E.: Essential Thrombophilia: Report of Five Cases, Arch. Int. Med. **59**:82 (Jan.) 1937. (*c*) Bergquist, G.: Ueber postoperative Thrombosen, Acta chir. Scandinav. **83**:415, 1940. (*d*) Brambel, C. E., and Loker, F. F.: Significance of Variations of Prothrombin Activity of Dilute Plasma, Proc. Soc. Exper. Biol. & Med. **53**:218, 1943. (*e*) de Takats, G.: Heparin Tolerance: A Test of the Clotting Mechanism, Surg., Gynec. & Obst. **77**:31, 1943. (*f*) Shapiro, S.: Hyperprothrombinemia: A Premonitory Sign of Thromboembolization (Description of a Method), Exper. Med. & Surg. **2**:103, 1944. (*g*) Ogura, J. H.; Fetter, N. R.; Blankenhorn, M. A., and Glueck, H. I.: Changes in Blood Coagulation Following Coronary Thrombosis Measured by Heparin Retarded Clotting Test (Waugh and Ruddick Test), J. Clin. Investigation **25**:586, 1946. (*h*) Tuft, H. S., and Rosenfield, R. E.: Detection of Intravascular Clotting Tendency by Heparin Tolerance Principle: Methods and Clinical Application, Am. J. Clin. Path. **17**:862, 1947. (*i*) Kadish, A. H.: Coagulation of the Blood in Lusteroid Tubes: A Study of Normal Persons and Patients with Arterial or Venous Thrombosis, Am. Heart J. **34**:212, 1947. (*j*) Vander Meer, Newman and Wright: Unpublished data, cited by Wright and Foley.[50d]

101. (*a*) Bancroft, Stanley-Brown and Chargaff.[79] (*b*) Ogura and others.[100g] Tuft and Rosenfield.[100h] (*c*) de Takats and Fowler.[93d] (*d*) Ochsner.[93e] (*e*) Shapiro, S.; Sherwin, B., and Gordimer, H.: Postoperative Thromboembolization: The Platelet Count and the Prothrombin Time After Surgical Operations; A Simple Method for Detecting Reductions and Elevations of Prothrombin Concentration (or Activity) of the Blood Plasma, Ann. Surg. **116**:175, 1942.

102. Shafiroff, B. G. P.; Doubilet, H.; Barcham, I. S., and Co Tui: The Coagulability of Venous Blood of Normal and Diseased Legs: A Study of One Hundred Ninety-One Subjects, Ann. Surg. **118**:482, 1943.

platelets occupy a leading role. Platelets in the process of lysis have also been shown to cause aged, inactive plasma to regain considerable clotting power (Roskam [9m]).

Accelerated platelet lysis, such as occurs in white thrombi, may explain the increased coagulability of the blood which has been reported to occur at the peak of the increase in platelets after operations,[103] after splenectomy,[100h] after myocardial infarction [100g] and during the platelet crises of essential thrombocythemia [104] or "essential thrombophilia" [100b]; more specifically, increased coagulability has been reported in the venous return from a limb already harboring a thrombus.[102] Furthermore, thrombin which is formed about white thrombi is probably carried off into the general circulation as long as some flow persists past the site of origin and may also account to some extent for increased clotting activity and platelet lability.

In accordance with Quick's [35b] postulate, as stated (that platelet lysis begets platelet lysis through the medium of accelerated thrombin formation), reduction in platelet lysis and, hence, in relative platelet adhesiveness during the administration of large doses of heparin sodium or dicumarol® may be explained as the direct result of an interruption of this chain reaction.

On the other hand, it should not be surprising if the rapid accumulation of large numbers of adhesive platelets as a localized white thrombus were to result in an absolute deficit of adhesive platelets in the circulating blood in the interval before the loss is replaced by regeneration. In actual experience, such rapid withdrawal of adhesive platelets from circulation can be demonstrated regularly during the formation of a large thrombus, particularly when platelet adhesiveness has been greatly increased beforehand, as in carcinoma. Thrombopenia secondary to thrombus formation in such cases may be extreme. This was seen, for example, in a patient dying of carcinoma of the stomach. In the last weeks of life, purpuric hemorrhages appeared in the skin and severe hemorrhage occurred from the carcinoma. The blood platelet count dropped to 147,000 per cubic millimeter and, later, to 62,000, with a pronounced decrease in adhesive platelets. The bleeding time became correspondingly prolonged (eleven and one-half to thirty-eight and one-half minutes). During that time, ischemic dry gangrene appeared in several toes, later followed by sudden hemiplegia and signs of pulmonary infarction. Massive thrombi were found at autopsy in the deep veins of the legs bilaterally, extending upward into the com-

103. Dawbarn, Earlam and Evans.[80n] Tuft and Rosenfield.[100h] Shapiro, Sherwin and Gordimer,[101e]

104. Evans, W. H.: The Blood Changes After Splenectomy in Splenic Anæmia, Purpura Hæmorrhagica and Acholuric Jaundice, with Special Reference to Platelets and Coagulation, J. Path. & Bact. **31**:815, 1928.

mon iliac vessels, from which multiple pulmonary emboli and infarcts had arisen. The right auricular appendage was filled with mural thrombus. In addition, thrombotic vegetations were present on the cusps of the aortic valve (nonbacterial thromboendocarditis) and were presumed to be the source of emboli to the brain and to the toes.

THROMBOPENIA SECONDARY TO PLATELET AGGLUTINATION

Multiple emboli composed of agglutinated platelets, produced by a variety of causes, may be associated with a similar tendency to thrombopenia. Intravascular agglutination of platelets, which cannot be prevented with heparin sodium,[74b] is reported to follow the intravenous injection of peptone and various colloids.[105] Intense but transitory thrombopenia accompanies this effect, which may result in purpura. Masses of agglutinated platelets plug the small vessels of many organs. Anaphylactic shock [106] and the injection of antiplatelet serum cause identical effects.[107] In man, multiple platelet thrombi of the minute vessels have been observed in fulminant purpura complicating meningococcus sepsis.[108] A rare but spectacular syndrome was also described by Moschcowitz [109]; it is characterized by febrile anemia and the widespread formation of hyaline thrombi in minute vessels. Although in his case petechial hemorrhages were the only purpuric manifestation, subsequent case reports have listed marked thrombopenic purpura and, in some instances, a leukemoid picture. Baehr, Klemperer and Schifrin [110] pointed out the origin of these thrombi in platelets withdrawn in myriads from the circulating blood. Singer [111] proposed the name "thrombotic thrombocytopenic purpura" for this disorder; Fitzgerald [112] suggested the term "thrombocytic acroangiothrombosis" to indicate the localization of the thrombi in the terminal vessels.

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105. Aynaud.[9c] Dameshek and Miller.[22]

106. Quick, Ota and Baronofsky.[74b] Biedl, A., and Kraus, R.: Experimentelle Studien über Anaphylaxie, Wien. klin. Wchnschr. **22**:363, 1909.

107. Aynaud.[9c] Le Sourd and Pagniez, cited by Aynaud.[9c] Tocantins, L. M., and Stewart, H. L.: Experimental Thrombopenic Purpura, Am. J. Path. **15**:1, 1939.

108. Hill, W. R., and Kinney, T. D.: The Cutaneous Lesions in Acute Meningococcemia: A Clinical and Pathologic Study, J. A. M. A. **134**:513 (June 7) 1947.

109. Moschcowitz, E.: An Acute Febrile Pleiochromic Anemia with Hyaline Thrombosis of the Terminal Arterioles and Capillaries, Arch. Int. Med. **36**:89 (July) 1925.

110. Baehr, G.; Klemperer, P., and Schifrin, A.: Acute Febrile Anemia and Thrombocytopenic Purpura with Diffuse Platelet Thrombosis of Capillaries and Arterioles, Tr. Am. Physicians **51**:43, 1936.

111. Singer, K.; Bornstein, F. P., and Wile, S. A.: Thrombotic Thrombocytopenic Purpura, Blood **2**:542, 1947.

112. Fitzgerald, P. J.; Auerbach, O., and Frame, E.: Thrombocytic Acroangiothrombosis (Platelet Thrombosis of the Capillaries, Arterioles, and Venules), Blood **2**:519, 1947.

PREDICTION AND DIAGNOSIS OF THROMBOSIS BY LABORATORY METHODS

Coagulation Tests.—The interest with which the problem of preclinical detection of thrombosis is regarded at present is reflected in the number and variety of tests which have been employed, although with inconstant success, in detecting the likelihood or actuality of thrombosis. The majority of these tests deal primarily with clotting factors, in accordance with the viewpoint that the underlying cause of thrombosis is an increase in circulating thromboplastin and in other elements concerned in the coagulation mechanism. According to certain writers, the coagulation time of whole blood [100c] or plasma [113] and the rate of conversion of prothrombin to thrombin are accelerated in patients manifesting a tendency to thrombosis. Shapiro [100f] and Brambel and Loker [100d] reported the existence of accelerated prothrombin time in diluted plasma, but this finding was not confirmed by Tuft and Rosenfield.[114] In most instances, prothrombin time has been measured in either whole or diluted plasma by the one stage method of Quick.[9k] Several factors besides absolute amount of prothrombin may be involved in accelerated coagulation and in accelerated formation of thrombin.[100d] These may include "accelerator globulin," [115] products of platelet lysis [36a,b] (enzymic [35b] or otherwise [116]), fibrinogen content [9k] and tissue and plasma thromboplastins.[9k] In general, these have been either ignored or included in the final result without specification.

The observation of increased heparin tolerance, as indicated by the coagulation time of blood taken after the intravenous administration of a standard test dose of heparin sodium (de Takats [100e]), parallels the common finding that higher therapeutic dosages of heparin sodium are needed to produce prolongation of coagulation time during a thromboembolic episode than in the normal state. A modification of the test in vitro was devised by Waugh and Ruddick [117] and further simplified by Tuft and Rosenfield.[100h]

113. Bancroft, Stanley-Brown and Chargaff.[79] Nygaard and Brown.[100b]

114. Tuft, H. S., and Rosenfield, R. E.: Significance of the Accelerated Reaction in Determination of Prothrombin Time of Diluted Plasma, Am. J. Clin. Path. **17**:704, 1947.

115. Ware, A. G.; Guest, M. M., and Seegers, W. H.: A Factor in Plasma Which Accelerates the Activation of Prothrombin, J. Biol. Chem. **169**:23, 1947. Ferguson, J. H., and Lewis, J. H.: "Accelerator Globulin" and "Anti-Hemophilic Globulin" in Thrombin Formation from Aged Plasma and in Hemophilic Blood, Proc. Soc. Exper. Biol. & Med. **67**:228, 1948.

116. Roskam.[9m] Eagle.[36c]

117. Waugh, T. R., and Ruddick, D. W.: A Test for Increased Coagulability of the Blood, Canad. M. A. J. **50**:547, 1944; Studies on Increased Coagulability of the Blood, ibid. **51**:11, 1944.

Not all observers are in agreement on the significance or reliability of these tests. Hurn, Barker and Mann [118] found no known specific coagulation factor to be conclusively implicated in thromboembolic disease, confirming the findings of Ewing,[119] Moses [65a] and Potts and Pearl.[120] Ogura,[100g] who found coagulability to be increased after coronary thrombosis, regarded it as result and not as cause, although possibly important in the propagation of the initial thrombus and in the formation of mural thrombi. Even the latter is of doubtful consequence in view of the fact that thrombi can form in the presence of reduced coagulability as well.[38d] The effectiveness of heparin sodium and dicumarol® in the prophylaxis and emergency treatment of thromboembolic disease depends primarily on a dosage sufficient to insure a pronounced reduction in clotting activity,[121] probably to the point of reducing platelet adhesiveness as well.[122]

Discrepancies in the observations just cited may possibly follow from the fact that no particularly decisive attempt has been made in most instances to correlate the laboratory data with the successive phases of thrombus development outlined previously. On the other hand, the fault may lie with the tests themselves. In a number of cases studied serially by us,[123] tests of platelet number and adhesiveness were made by a method to be described in this paper (the glass wool filter test) and simultaneous companion studies were made of prothrombin time, heparin tolerance in vitro [100h] and clot retraction time.[97a] In several of these cases, the results were consistent with clinical or other evidences which suggested developing or developed thrombosis. In other instances, the results of the coagulation tests were at variance with one another and with those of our own test. In general, coagulation tests proved less dependable than studies of blood platelets.

118. Hurn, M.; Barker, N. W., and Mann, F. D.: Variations in Prothrombin and Antithrombin in Patients with Thrombosing Tendencies, Am. J. Clin. Path. **17**:709, 1947.

119. Ewing, M. E.; Cullimore, O. W., and Blatherwick, N. R.: Plasma Clotting Time and Serum Calcium of Patients Recovered from Attacks of Coronary Thrombosis, Proc. Soc. Exper. Biol. & Med. **47**:23, 1941.

120. Potts, W. J., and Pearl, E.: A Study of the Platelet Count and the Coagulation Time of Plasma and Whole Blood Following Operation, Surg., Gynec. & Obst. **73**:492, 1941.

121. (*a*) Jorpes.[44a] (*b*) Allen, E. V.: The Clinical Use of Anticoagulants: Report of Treatment with Dicumarol in 1,686 Postoperative Cases, J. A. M. A. **134**:323 (May 24) 1947.

122. Tocantins.[9g] Quick, A. J.: The Anticoagulants Effective in Vivo with Special Reference to Heparin and Dicumarol, Physiol. Rev. **24**:297, 1944.

123. Moolten, S. E., and Vroman, L.: The Adhesiveness of Blood Platelets in Thromboembolism and Hemorrhagic Disorders: I. Measurement of Adhesiveness by the Glass-Wool Filter, Am. J. Clin. Path. **19**:701, 1949. Moolten, S. E.; Vroman, L., Vroman, G. M. S.: The Adhesiveness of Blood Platelets in Thromboembolism and Hemorrhagic Disorders: II. Diagnostic and Prognostic Significance of Platelet Adhesiveness, ibid. **19**:814, 1949.

Blood Platelet Counts.—Several writers [124] have commented on the association of high platelet counts and the increased incidence of thromboembolism, either as a transient occurrence, after operation, post partum or otherwise, or as a persistent trait.[125] Impressive examples of recurrent thrombosis related to chronically increased platelet formation may be encountered in certain cases of carcinoma (Trousseau's sign [126]), of polycythemia vera [127] and of essential thrombocythemia.[128] These conditions can perhaps best be considered together under the comprehensive title of "thrombophilia" (originally applied in cases of migratory thrombophlebitis [129]). Many workers have been inclined to disregard the association between platelet count and thrombosis as no more than fortuitous [130] except in extreme instances or as incidental to some other, more basic factor.[131] Just as even severe thrombopenia may exist without an abnormal tendency to bleed (Macfarlane,[17] Roskam,[9m] Rosenthal [69g]), so thrombocytosis of pronounced degree may occur without an increased tendency to thrombosis (Normann,[132] Adams [80d] and others [133]). On the other hand, a quick drop in the platelet count has been reported as a warning sign of thrombosis.[134] Absence of the usual postoperative or postinfectious rise has been accorded similar significance.[80f]

Tests of Platelet Agglutinability and Adhesiveness in Thromboembolism.—Evidence has now accumulated in ample measure that a

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124. Welch.[8c] Aschoff.[8d] Olef.[66l] Hartmann.[73] Footnote 80. Tuft and Rosenfield.[100h] Shapiro, Sherwin and Gardimer.[101e]

125. (*a*) Olef.[66l] (*b*) Rosenthal.[69c] (*c*) Nygaard and Brown.[100b] (*d*) Rosenthal, N.: Clinical and Hematologic Studies on Banti's Disease: I. The Blood Platelet Factor with Reference to Splenectomy, J. A. M. A. **84**:1887 (June 20) 1925.

126. Osler.[6] Cited by Welch.[8c] Hayem.[37f]

127. Rosenthal.[91] Olef.[66l] Norman, I. L., and Allen, E. V.: The Vascular Complications of Polycythemia, Am. Heart J. **13**:257, 1937.

128. Rosenthal.[69g] Nygaard and Brown.[100b] Evans.[104] Rosenthal.[125d]

129. Mendel, F.: Ueber "Thrombophilie" und das Frühaufstehen der Wöchnerinnen und Laparotomierten, München. med. Wchnschr. **56**:2149, 1909.

130. (*a*) Allen, Barker and Hines.[50a] (*b*) Moses.[65a] (*c*) Potts and Pearl.[120] (*d*) Windfeld, P.: Beiträge zur Kenntnis der postoperativen Blutveränderungen, Acta chir. Scandinav. (supp. 25) **70**:1, 1933.

131. Aschoff.[8d] Wright.[13d] Adams.[80d] Belt, T. H.: Thrombosis and Pulmonary Embolism, Am. J. Path. **10**:129, 1934.

132. Normann, E.: Wie verhalten sich die Thrombocyten nach operativ behandelten Krankheitsfällen und bei der Entstehung postoperativer Thrombose? Deutsche Ztschr. f. Chir. **212**:166, 1928.

133. (*a*) Uotila.[69h] (*b*) Mackay.[72g] (*c*) Windfeld.[130d] (*d*) Di Guglielmo, G.: Eritroleucemia e piastrinemia, Folia med. **6**:1, 36, 55, 81 and 101, 1920.

134. (*a*) Kristenson.[37j] (*b*) Kojima.[38g] (*c*) Rosenthal.[125d] (*d*) Norman.[132] (*e*) Kristenson, A.: Beobachtungen über die Thrombozytenzahl bei klinischer Venenthrombose, Acta med. Scandinav. **69**:453, 1928. (*f*) Woodruff, P.: The Behaviour of the Blood Platelets in Thyreotoxicosis, M. J. Australia **2**:190, 1940.

relation exists between the increased stickiness of platelets and an abnormal susceptibility to thrombus formation. Von Seemen and Binswanger [44e] were among the first to report an increase in platelet agglutinability in patients recovering from surgical procedures. They employed a method, devised by Bürker [135] in 1903, which consisted in moist chamber observation of the platelets contained in plasma separating from a drop of finger blood collected in a paraffin cup to avoid clotting. According to them, platelets clumped in the greatest volume and speed three to six days after operation. A more elaborate method based on the same principle was devised by Jürgens and Naumann [138]: Platelets were obtained in a suspension of plasma by permitting venous blood, unmixed with anticoagulant, to sediment quietly at refrigerator temperature in a paraffin-lined tube. Øllgaard [68c] developed a macroscopic method in which platelet agglutinability was measured by determining the minimal amount of solution of mercuric chloride capable of producing visible flocculation of platelets suspended in citrated plasma and previously "stabilized" by being heated on a water bath at 42 C. for three hours. In Copley's method,[136] platelets are stabilized by thorough washing in sodium chloride solution and are added to various plasmas for comparative macroscopic tests of agglutinability.

Platelet adhesiveness to a glass surface was measured by Morawitz and Jürgens [137] by determining the time required for a glass capillary tube to become plugged while blood was forced back and forth through it by means of a pumping device ("capillary thrombometer"). In a simpler and more reliable method, later devised by Wright,[9h] platelet adhesiveness is calculated as the rate of loss of platelets from a measured sample of heparinized blood by their deposition on a glass surface. For this purpose she employed a specially designed, slowly rotating tube of glass, coated internally with paraffin, in which the specimen of blood is constantly passed over two small windows of uncoated glass during a period of eighty minutes. Platelet counts are made at intervals of twenty minutes.

Increased platelet agglutination has been encountered in a variety of clinical conditions. Øllgaard [68c] found it increased, by his method, in many patients with acute febrile disease, in postoperative patients and in patients with thromboembolism; the administration of heparin sodium had an inhibitory effect. Morawitz and Jürgens [137] reported increased

135. Bürker, K.: Eine einfache Methode zur Gewinnung von Blutplättchen, Centralbl. f. Physiol. **17**:137, 1903.

136. Footnote 68 *d*, *e* and *f*.

137. Morawitz, P., and Jürgens, R.: Gibt es Thrombasthenie? Muenchen. med. Wchnschr. **77**:2001, 1930; cited by Morawitz, P.: Thrombose, Verhandl. d. deutsch. Gesellsch. f. Kreislaufforsch. 1930; **7**:80, 1934.

platelet adhesiveness in infections and in recurrent thrombosis which complicated polycythemia vera associated with hyperthrombocytosis, but not in ordinary "spontaneous" thrombosis. With the rotating tube, Wright [13d] found adhesiveness regularly increased after operations and childbirth, paralleling in its rise and subsequent fall the curve of incidence of thromboembolism. The addition of anticoagulants to blood in vitro and the administration to human subjects of sufficient dicumarol® to produce hypoprothrombinemia brought about a significant lowering of platelet adhesiveness.[13g] By means of her method, Wright succeeded in translating into numerical units the principles of platelet adhesiveness which had been developed along various experimental lines, including the action thereon of anticoagulants, by Bizzozero [4] (1882), Bürker [9b] (1904), Deetjen [9d] (1909), Shionoya [34b] (1927), Best, Cowan and Maclean [10b] (1938) and Dale and Jaques [10d] (1942).

THE GLASS WOOL FILTER TEST

In the course of our primary studies on the action of thrombocytosin and thrombocytopen on blood platelets in vitro,[76] it was found necessary to improvise a test of platelet adhesiveness with which one could detect relatively small changes in this property. Glass wool (fiberglas®) was found to be serviceable in providing a maximum of glass surface for the blood sample being tested.

Procedure.—In the standardized procedure followed at the time of this report,[123] glass wool is braided into a wick, cleansed with acetone, cut into a convenient length and inserted into the upper end of a test tube, from the mouth of which it is suspended freely by two arms of a Y made by splitting its upper part. The "filter" is moistened with sodium chloride solution, capped to prevent drying and brought to incubator temperature. Blood is drawn from a vein into a silicone-coated syringe containing sufficient sodium citrate to make a final concentration of 0.38 per cent. After a sample is removed for erythrocyte and platelet counts, 1 cc. is taken up in a pipet, allowed to drip into the prepared filter (in which it is kept exactly thirty seconds) and then washed through with chilled sodium chloride solution containing 0.38 per cent sodium citrate. Erythrocyte and platelet counts are made from the filter washings and the results corrected for dilution against the prefiltration sample as a control. From these data, the number of platelets lost to the filter is easily computed and a factor is obtained for platelet adhesiveness ("adhesive index"). From this, the proportion of adhesive platelets can be computed with a simple formula. With the test properly standardized, a surprisingly stable level of adhesive platelets is found in normal persons, ranging between 60,000 and 110,000 adhesive platelets per cubic millimeter. In serial tests, the fluctuations within this range are normally of the same order as those of the total platelet count.

138. (*a*) Wright.[9h] (*b*) Spooner, M., and Meyer, O. O.: The Effect of Dicumarol (3,3'-Methylenebis 4-Hydroxycoumarin) on Platelet Adhesiveness, Am. J. Physiol. **142**:279, 1944. (*c*) Weiner, M.; Zeltmacher, K.; Reich, C., and Shapiro, S.: Platelet Adhesiveness, Blood **3**:1275, 1948.

CLINICAL CORRELATIONS WITH INCREASED PLATELET ADHESIVENESS

The glass wool filter test for platelet adhesiveness was employed in a variety of clinical conditions in conjunction with other diagnostic procedures applicable to the study of thrombosis and of disorders of hemostasis. The results of the survey appear to strengthen the viewpoint that qualitative changes in the blood platelets have greater significance than numerical changes. Increased platelet adhesiveness was found to be an almost constant accompaniment of cellular destruction anywhere in the body and to be generally, but not always, associated with a rise in the total platelet count. Similar findings were recorded in human subjects on a diet high in animal fats, including milk fat and egg yolk. Thrombocytosin (usually obtained from egg yolk) reproduced these findings in the rabbit and in human patients with purpura.

Surgical and Accidental Trauma.—As noted by Wright[13d] and others,[139] platelet number and adhesiveness were generally observed to rise during convalescence from surgical operations or extensive trauma. In many instances, a slight rise in both factors appeared as early as one or two hours after operation, followed by a moderate fall which was perhaps indicative of increased utilization of platelets in the formation of wound thrombi. Beginning, as a rule, three to five days after operation, the total count and adhesiveness tended to rise progressively during a certain period and then fell gradually to normal. Similar findings were recorded after accidental trauma, especially fracture or severe contusion. Exceptions to this pattern of platelet behavior were not uncommon in this group; in certain instances, it was possible to demonstrate the presence of complications, particularly thrombosis.

Ischemic Necrosis (Myocardial Infarction, Peripheral Vascular Gangrene and Pulmonary Infarction).—These conditions were regularly accompanied, at least in their early stages, by a rise in platelet adhesiveness rivaling or surpassing that observed after operation. The total platelet count was often elevated as well, although not necessarily in corresponding degree. Later in the course of the acute stage, diminished counts, particularly of adhesive platelets, usually portended the formation of fresh thrombi of large size, e. g., venous thrombi in the lower limbs or mural thrombi within the infarcted ventricle. The application of the platelet tests, particularly serial tests, was of much value in the diagnosis of recent myocardial infarction, especially before electrocardiographic confirmation, and as an indication for the administration of heparin sodium and dicumarol,® as described later in this paper.

139. Starlinger and Sametnik.[28] Lampert.[30f] von Seemen and Binswanger.[44e] Spooner and Meyer.[188b]

Cutaneous Irritation.—As mentioned previously, extensive dermatitis, cutaneous irritation by chemical or physical agents or injections of bacterial or chemical irritants into the subcutaneous tissues have long been known to evoke a sharp rise in the platelet count.[140] All patients with dermatitis and cellulitis studied by the glass wool filter test were observed to show, in addition, a considerable increase in platelet adhesiveness.

Cancer.—A number of cases of cancer of various organs were studied by this method. In all, the adhesiveness of blood platelets was persistently high, although the total count was only moderately elevated or normal. Complicating thrombosis was observed in several of these cases, unrelated to surgical intervention and involving not only the peripheral veins but, in 1 case, the cardiac valves and the auricular appendage as well, as indicated previously. In our experience, the predisposition to thromboembolic disease in cancer appears to be more closely related to platelet adhesiveness than to total count. This observation may warrant inclusion among the indications for prophylactic use of anticoagulants, particularly after surgical procedures. Aside from its probable prognostic value in evaluating the possibilities of thromboembolism in proved cases of carcinoma, the determination of persistently high platelet adhesiveness may prove helpful in the differential diagnosis of suspected cancer in the absence of pathognomonic signs and in the early detection of occult cancer. A decisive correlation between high platelet adhesiveness and undiscovered cancer may be anticipated a priori in carcinoma of the pancreas, in which thrombotic incidents are notoriously common.[141] On theoretic grounds, thrombosis may be explained by the fact that the tumor cells continue to produce secretion which, having no means of egress to the intestine, exerts a digestive action on the gland itself, reflected in the presence of mucinous foci.[141b] By the same mechanism, local areas of lipolysis and fat necrosis[142] may appear, resulting in the mobilization of thrombocytosin. The circulation of pancreatic enzymes (particularly lipase) in the blood stream, which is observed to be increased in this disease,[143] may contribute considerably to

140. Footnote 82. Bunting.[83]

141. (*a*) Sproul, E. E.: Carcinoma and Venous Thrombosis: The Frequency of Association of Carcinoma in the Body or Tail of the Pancreas with Multiple Venous Thrombosis, Am. J. Cancer **34**:566, 1938. (*b*) Kenney, W. E.: The Association of Carcinoma in the Body and Tail of the Pancreas with Multiple Venous Thrombi, Surgery **14**:600, 1943.

142. Titone, M.: Ueber ungewöhnlich ausgebreitete Fettgewebs- und Gewebsnekrosen bei Pankreaskrebs, Virchows Arch. f. path. Anat. **297**:416, 1936.

143. Comfort, M. W., and Osterberg, A. E.: The Value of Determination of the Concentration of Serum Amylase and Serum Lipase in the Diagnosis of Disease of the Pancreas, Proc. Staff Meet., Mayo Clin. **15**:429, 1940.

the mobilization of thrombocytosin from adipose tissue and, in addition, exert a detergent action resulting in the development of endothelial wettability.

Thrombocythemia.—A few patients were encountered in whom persistently high platelet count and adhesiveness, together with the tendency to recurrent thrombus formation, could not be explained by any of the several factors just enumerated. In these instances, the hematologic findings signalized a primary affection of the bone marrow. Erythremia (polycythemia vera) was diagnosed in 1 patient presenting residua of cerebral and coronary thromboses; thrombotic gangrene of one foot eventually necessitated amputation of the leg. In this case, the highest erythrocyte count observed was only 6,470,000 per cubic millimeter; yet, the number of platelets rose to 1,224,000 per cubic millimeter, nearly all of which (1,126,000) were adhesive, and sternal aspiration revealed an exceptional number and segmentation activity of the megakaryocytes. Paradoxically, the patient suffered from repeated attacks of deep subcutaneous hemorrhage causing enormous painful hematomas. In another patient, gangrene of the leg followed thrombosis of the femoral artery complicated by a propagating thrombus of the accompanying vein. Although she presented no evidence of polycythemia at the time, the peripheral blood exhibited a striking leukemoid reaction in the course of secondary infection of the amputation stump, the leukocyte count reaching 95,000 per cubic millimeter, with a high proportion of myelocytes. The blood platelet count was excessive, rising to 702,000 cells per cubic millimeter, of which about 40 per cent were adhesive. At autopsy, nodular myeloid hyperplasia was demonstrated in the bone marrow, unassociated with evidences of leukemia; multiple benign tumors were present in the liver (cholangiomas), and a benign hypernephroid tumor was found in one kidney. In a third patient, a young woman of 31, neither erythroid nor myeloid overgrowth was present, the entire picture being that of "idiopathic thrombocythemia" (Rosenthal [69g]) complicated by thrombosis of the splenic vein, which caused a succession of attacks of painful swelling of the spleen leading to its permanent marked enlargement. The platelet count initially was 580,000 per cubic millimeter, with a high proportion of adhesive platelets. After removal of the spleen, which was about ten times normal size (its weight was 1,100 Gm.), the platelet count rose to 2,800,000, with a corresponding rise in the proportion of adhesive platelets. During several months' observation subsequently, little change was noted in the persistently high platelet number and platelet adhesiveness and the patient remained clinically free of thrombosis. Surprisingly, however, she manifested chronic gingival bleeding and occasional purpura of the skin. The bleeding time was somewhat prolonged and the capillaries of the nail fold, viewed microscopically, were widely

dilated and somewhat tortuous, recalling the findings considered characteristic of idiopathic thrombopenic purpura.[17] As in the patient with erythremia previously mentioned, the hemorrhagic tendency appeared to be independent of platelet count and adhesiveness, both of which were exceptionally high. It is difficult to reconcile this apparent discrepancy except by speculation based on analogy. If a comparison is made with certain benign tumors, the possibility may be suggested that these conditions, individually or in their collective form (erythroleukemia, as described by di Guglielmo [133d]), represent the counterpart in the bone marrow of benign tumors of other tissues, being characterized by excessive proliferation of one or more hematic cell strains and by correspondingly defective functional worth and impaired capacity to respond to the normal controlling influences of the body, among which may be included the action of the splenic hormone. The analogy is strengthened by the frequency with which erythremia or erythroleukemia terminates in true leukemia.[144] At present, studies are being undertaken to test the hypothesis that the functional defect in the platelets responsible for bleeding in these cases [145] resides in their vasoconstrictor elements.

Thrombosis and Embolism.—Although thromboses which were recognized clinically or proved at autopsy developed in only a minority of patients in the preceding categories, sufficient data were accumulated to justify the following generalizations:

1. A rising or persistently elevated count of adhesive platelets in the circulating blood is a consistent laboratory finding in the prodromal phases of thrombosis. An elevation of the total platelet count is frequently, but not regularly, present.

2. A rapid fall in the platelet count, comprising chiefly a drop in the number of adhesive platelets, often coincides with the formation of a white thrombus.

Information is still lacking on the minimal size of a white thrombus required to produce an unmistakable change in the platelet picture. Present data suggest that only thrombi forming in large veins and mural thrombi of the cardiac chambers affect the count significantly.

The time between a drop in the platelet count and the earliest signs of manifest thrombosis is also indeterminate. In general, signs of pulmonary embolism or infarction, reflecting the detachment of red thrombi from foci still clinically silent locally, first came to our notice three or more days after a fall in the platelet count had begun. Several days more elapsed, as a rule, before local signs of phlebitis were recognized.

144. Rosenthal.[69e] Rosenthal, N., and Bassen, F. A.: Course of Polycythemia, Arch. Int. Med. **62**:1903 (Dec.) 1938.

145. Footnote 69 *f*, *g* and *h*. Tinney, W. S., and Giffin, H. Z.: Hematologic Complications of Polycythemia Vera, Proc. Staff Meet., Mayo Clin. **18**:227, 1943.

A cyclic platelet curve was observed in patients with large propagating venous thrombi which gave rise to recurrent emboli and infarcts of the lung.

On several occasions, a transient fall in both platelet count and platelet adhesiveness was encountered in predisposed patients without subsequent confirmatory signs or symptoms of thrombus formation. These instances were interpreted as probably the result of "silent thrombosis," comprising either nonobstructing mural platelet thrombi or occluding mixed thrombi of moderate size which resolve or undergo quiet organization and first come to light much later as the cause of superficial varicose veins. The frequency of such inapparent thromboses with or without undetected pulmonary embolism is now recognized as much higher than that of manifest thrombosis. Rössle [58a] reported in 1937 an incidence, as observed at autopsy, of thrombi of the veins of the calf in 27.1 per cent of persons over 20. Neumann [93f] (1938) reported venous thrombi in 100 of 165 consecutive autopsies, and Hunter and his associates [44b] (1945) demonstrated deep venous thromboses in the legs of over 50 per cent of 400 adults at autopsy. On the other hand, clinically manifest thrombotic disease was reported by Barker and Priestley [146] to follow 0.96 per cent of all operations, about 2 per cent of laparotomies and 3 per cent of operations on the female pelvis. On the basis of the previous data, it may be estimated that only about 2 per cent of calf vein thrombi occurring in persons convalescing from operations actually become clinically demonstrable, either in situ or by reason of embolism.

Tests of blood coagulability often paralleled changes in platelet count and adhesiveness, but many discordant results were obtained. In several cases, comparative serial studies were made of prothrombin time (Quick), heparin tolerance (in vitro) [100b] and clot retraction time.[97a] From an analysis of time relationships, it seems likely that increased activity of clotting factors in the circulating blood can be explained in large part as the result of increased lysis of blood platelets (probably in the substance of developing white thrombi), resulting, in turn, in the accelerated conversion of prothrombin to thrombin at such sites. Increased clotting activity occasionally developed abruptly in the wake of a sharp rise in platelet count and adhesiveness. During the phase of thrombus development, mirrored in a fall in adhesive platelets, tests of clotting activity were often at variance but exhibited a downward trend in many instances, possibly as an indication of the withdrawal of clotting factors in the formation of large red thrombi.

146. Barker, N. W., and Priestley, J. T.: A Statistical Study of Postoperative Venous Thrombosis and Pulmonary Embolism: I. Incidence in Various Types of Operations, Proc. Staff Meet., Mayo Clin. **15**:769, 1940.

Administration of Heparin Sodium and Dicumarol.®—Coincidentally with the administration of heparin sodium in sufficient dosage to prolong coagulation time to a range of fifteen to thirty minutes or longer, the number of adhesive platelets dropped promptly from a high level to normal or below in each of the patients tested. In 1 case, ordinary doses of heparin sodium caused the apparent disappearance of all adhesive platelets. The total count tended to rise concurrently with a fall in adhesiveness. On the withdrawal of heparin sodium, the adhesive count returned to its previous level or higher and the total count dropped proportionately. The heparin-induced rise in the total count was interpreted as the prolonged survival of platelets in circulation due to reduced lysis, which was the result of the inhibited formation of thrombin, the normal activator of platelet adhesiveness and lysis.[35b] The post-heparin rebound in the adhesive platelet count was accompanied in these patients with shortened prothrombin time, which was attributed to accelerated platelet lysis, and hence to increased liberation of the platelet accelerator[36a, b] of prothrombin activation. A fall in total platelet count through heparinization has not yet been encountered in human beings, contrary to Copley's observations in dogs and hamsters (but not in mice).[69d]

A moderate fall in platelet adhesiveness was observed in patients treated with dicumarol® in whom prothrombin activity had been maintained inadvertently for three days or longer at levels recorded as "less than 10 per cent." The platelet adhesiveness dropped in such cases into the lower range of normal but not below, in contrast to the striking drop below normal obtained with heparin sodium.

The prophylactic value of heparin sodium and dicumarol® has been established beyond dispute, and their use has contributed to a spectacular lowering of the incidence and mortality rate of thromboembolism following surgical intervention.[147] A similar program is apparently bearing fruit in the field of cardiology[148] and peripheral vascular disease.[149]

147. Murray and others.[37h] Jorpes.[44a] Allen, Barker and Hines.[50a] Bauer.[93c] Allen.[121b] Barker, N. W.; Hines, E. A., Jr.; Kvale, W. F., and Allen, E. V.: Dicumarol: Its Action, Clinical Use and Effectiveness as an Anticoagulant Drug, Am. J. Med. **3**:634, 1947.

148. Wright and Foley.[50d] Nichol, E. S., and Page, S. W., Jr.: Dicumarol Therapy in Acute Coronary Thrombosis: Results in Fifty Attacks, with Review of Data on Embolic Complications and Immediate Mortality in Myocardial Infarction, Florida M. A. J. **32**:365, 1946. Peters, H. R.; Guyther, J. R., and Brambel, C. E.: Dicumarol in Acute Coronary Thrombosis, J. A. M. A. **130**:398 (Feb. 16) 1946.

149. Allen, Barker and Hines.[50a] Lange and Boyd.[57] Brambel, C. E., and Loker, F.: Application of Dicoumarin (3,3'-Methylene-Bis-[4-Hydroxycoumarin]) in Trauma and Gangrene, Arch. Surg. **48**:1 (Jan.) 1944. Lange, K., and Loewe, L.: Subcutaneous Heparin in Pitkin Menstruum for Treatment of Experimental

The effect of anticoagulants is probably twofold: (1) the retardation of clotting, restricting the formation and propagation of red thrombi, and (2) the reduction of platelet adhesiveness, restricting the formation of white thrombi. Both effects, in the last analysis, represent the suppressive action of these agents on the formation of thrombin, as previously indicated. Certain clinical and experimental data suggest, in addition, that these agents favor the resolution of red thrombi already formed.[150] According to von Kaulla,[151] the role of plasma proteases having fibrinolytic activity deserves further study in relation to the spontaneous disappearance of thrombi. Morawitz[152] apparently also anticipated the possibility that thrombi already formed may dissolve under the action of a specific fibrinolytic ferment, at least in the hemorrhagic tendency induced by phosphorus necrosis of the liver. Although Ferguson and Glazko[153] attributed antiproteolytic properties to heparin, Horwitt[154] indicated that that effect is relatively slight in the case of ordinary doses of heparin sodium and probably does not constitute part of its physiologic action. Accordingly, it may be postulated that heparin sodium not only inactivates and blocks the production of thrombin but leaves undisturbed the continued activity of fibrinolytic (and thrombinolytic?) enzymes previously liberated in the initiation of the clotting process, explaining thereby the apparent clot-dissolving property of heparin sodium in the case of red thrombi. From experimental observations, Loewe and others[150b] concluded that dicumarol® also favors the resolution of thrombi, although much less effectively than heparin sodium.

Attempts to established standards of dosage for heparin sodium and dicumarol® based on changes induced in platelet adhesiveness proved unsuccessful in our experience. No advantage was found in employing the fall of platelet adhesiveness as a criterion of effective dosage of

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Human Frostbite, Surg., Gynec. & Obst. **82**:256, 1946. McLean, J., and Johnson, A. B.: Gangrene Following Fracture Treated with Heparin, Papaverine and Intermittent Venous Occlusion: Report of Case; Reasons for Using Heparin, Surgery **20**:324, 1946. Allen, E. V.: The Emergency Treatment of Vascular Occlusions, J. A. M. A. **135**:15 (Sept. 6) 1947.

150. (*a*) Rabinovitch, J., and Pines, B.: Effect of Heparin on Experimentally Produced Venous Thrombosis, Surgery **14**:669, 1943. (*b*) Loewe, L.; Hirsch, E.; Grayzel, D. M., and Kashdan, F.: Experimental Study of the Comparative Action of Heparin and Dicumarol on the in Vivo Clot, J. Lab. & Clin. Med. **33**:721, 1948.

151. von Kaulla, K. N.: Betrachtungen zur postnarkotischen Fibrinolyse, Schweiz. med. Wchnschr. **77**:313, 1947.

152. Morawitz, cited by Frank.[691]

153. Ferguson, J. H., and Glazko, A. J.: Heparin and Natural Antiprothrombin in Relation to Activation and "Assay" of Prothrombin, Am. J. Physiol. **134**:47, 1941.

154. Horwitt, M. K.: Trypsin and Chymotrypsin Versus Heparin, Science **101**:376, 1945.

heparin sodium over the use of standard methods for measuring coagulation time. On the other hand, abnormal bleeding following the administration of either heparin sodium or dicumarol® appeared in certain cases in which the dosage was insufficient to reduce platelet adhesiveness below normal. On the withdrawal of anticoagulants, the prolongation of bleeding time occasionally persisted long after the coagulation time, prothrombin time and platelet adhesiveness had returned to their previous level.

The occurrence of a bleeding tendency in the presence of normal coagulation time, normal prothrombin time and normal or elevated platelet adhesiveness, as in the instances mentioned, introduces the possibility that the underlying fault lies within the blood vessels. Heparin sodium given to mice was reported by Copley and Lalich [155] to cause prolonged bleeding time when given in excessive doses; the result was attributed to the exhaustion of an unidentified factor in the tissues. The experiments of Rigdon and Wilson [156] suggest that heparin sodium has no effect on capillary permeability as such or on the development of inflammation. Generalized vasodilatation has been produced experimentally by overdosage with dicumarol® (Bingham [157]; Dale and Jaques [10d]). Suggestive data have also been obtained with hirudin. Jürgens cited Roskam's experiments and his own [9j] to show a direct action of hirudin on endothelium which parallels or exceeds its effect on platelets, being prolonged beyond the duration of the latter and preventing platelet agglutination and the attachment of clot to traumatized endothelium and contiguous wound surfaces.

An alternative possibility which may deserve further study involves the concept of the blood platelet as a "solid secretion" which undergoes physiologic breakdown to liberate a vasoconstrictor substance in support of normal vascular contractility and tonus, as mentioned previously. It remains to be shown whether or not heparin and other anticoagulants effective in vivo exert their effect on blood vessels indirectly, perhaps by impairing the biologic effectiveness of blood platelets as a source of a vasoconstrictor substance. It is conceivable that if such an effect can be demonstrated it may occur selectively, without the impairment of adhesiveness or other known properties of platelets. The possibility that such dissociation in platelet properties may exist is suggested by the described findings in erythremia and idiopathic thrombocythemia.

155. Copley, A. L., and Lalich, J. J.: The Experimental Production of a Hemophilia-like Condition in Heparinized Mice, Am. J. Physiol. **135**:547, 1942.

156. Rigdon, R. H., and Wilson, H.: Capillary Permeability and Inflammation in Rabbits Given Heparin, Arch. Surg. **43**:64 (July) 1941.

157. Bingham, J. B.; Meyer, O. O., and Pohle, F. J.: Studies on the Hemorrhagic Agent 3,3'-Methylene-Bis-(4-Hydroxycoumarin): I. Its Effect on the Prothrombin and Coagulation Time of the Blood of Dogs and Humans, Am. J. M. Sc. **202**:563, 1941.

POSSIBLE ROLE OF SPLEEN IN PREVENTION OF FORMATION OF WHITE THROMBUS

The premise that the spleen normally plays a part in protecting the circulation against intravascular thrombi is supported by a variety of evidence. Surgical removal of the spleen is followed by a greater incidence of distant thrombosis than any other operation of equivalent magnitude.[158] Although a pronounced rise in the platelet count occurs after splenectomy, the determining factor in thrombosis is more likely the qualitative alterations in platelets (referred to previously), manifested as increased agglutinability and adhesiveness. Rosenthal, who was one of the first to suggest that the role of the spleen in purpura was bound up with its power to alter the quality of the blood platelets,[69f] also posulated an active role of the spleen in suppressing thrombus formation in patients with an excessively high platelet count (idiopathic thrombocythemia [159]). Removal of the spleen in cases of thrombopenic purpura has been shown repeatedly to result in permanent cure of the bleeding tendency even when the platelet count returns to its former low level,[160] adding further weight to Rosenthal's concept that the spleen is concerned with the quality of the platelets. It is reasonable, therefore, to postulate that deficient function of the spleen may be one of the predisposing factors in thromboembolism and that excessive function of the spleen ("hypersplenism") may suppress the formation of thrombi by its effect on platelet qualities, even to the point of inducing a hemorrhagic tendency. This is an extension of the old theory of a suppressive splenic hormone.[161]

Our studies of platelet adhesiveness in thrombopenic purpura appear to lend support to the general concept of hypersplenism. In the "idiopathic" type, presumably caused by hyperfunction of the spleen, platelet adhesiveness was found to be extremely low or virtually absent. A similar state was encountered in a case of splenomegaly complicating coarse nodular cirrhosis. In "secondary" thrombopenic purpura resulting from leukemic infiltration of the bone marrow (and spleen), platelet adhesiveness was undiminished or relatively increased, despite the marked lowering of the total platelet count. These data suggest that

158. Allen, Barker and Hines.[50a] Barker and Priestly.[146]

159. Rosenthal.[69e] Rosenthal.[125d]

160. Jürgens.[11d] Jürgens and Graupner.[66f] Brill and Rosenthal.[69d] Rosenthal.[69e] Footnote 71 *c* and *d*.

161. (*a*) Frank.[12e] (*b*) Frank.[69i] (*c*) Footnote 86 *c*, *d* and *e*. (*d*) Isaac (1912); Türk; Naegeli; Bock and Franzel; Jombres; Buchem; cited by Hirschboeck, J. S.: Hematologic Effects of Splenectomy in Still-Chauffard-Felty Syndrome: A Report of Two Cases, Blood **1**:247, 1946. (*e*) Engelbreth-Holm, J.: A Study of Tuberculous Splenomegaly and Splenogenic Controlling of the Cell Emission from the Bone Marrow, Am. J. M. Sc. **195**:32, 1938.

two separate mechanisms underlie most instances of thrombopenia: (1) hormonal suppression of megakaryocytic segmentation and (2) quantitative reduction in the number of megakaryocytes. The former results in both qualitative and quantitative changes in blood platelets; the latter, in quantitative changes alone. This difference in mechanism may account for the greater tendency to hemorrhage in hypersplenic purpura than in secondary purpuras having a similar numerical platelet count.[18f]

The presence of thrombopenia and hemorrhagic tendency in certain systemic infections as well as in "idiopathic" thrombopenic purpura suggests a common background of hyperplasia of the elements in the spleen which are comprised in the reticuloendothelial system. In general, such infections may be classified as proliferative reticuloendotheliloses, characterized in their florid stages by anergy rather than allergy, and by systematization rather than localization or encapsulation.[162] In this group may be included infectious mononucleosis,[163] brucellosis,[163c] typhoid,[69k] abdominal lymphogranulomatosis,[164] malaria,[69k] sarcoidosis,[165] miliary tuberculosis,[166] kala-azar,[167] Felty's syndrome [168] and long-standing Streptococcus viridans endocarditis.[169] In most instances, thrombopenia is moderate; purpura is an infrequent complication but may be severe. Leukopenia is also common; yet, extreme granulocytopenia is rare except, perhaps, in kala-azar.[167] In infectious mono-

162. Moolten, S. E.: Characterization of Systemic Infection Which Is Principally Proliferative (The Pattern of Infectious Reticulo-Endotheliosis), Lecture XV, An Interpretive Course in Pathology for the Clinician, New Brunswick, N. J., Rutgers University, 1947. Mimeographed copies available from the author.

163. (*a*) Rosenthal.[71c] (*b*) Magner, W., and Brooks, E. F.: Infection Mononucleosis with Acute Thrombopenic Purpura, Bull. Acad. Med. Toronto **15**:189, 1942. (*c*) Damashek, W., and Grassi, M. A.: Infectious Lymphadenosis ("Mononucleosis") and Thrombocytopenic Purpura: Recovery After Splenectomy, Blood **1**:339, 1946.

164. Frank.[69l] Schousboe.[86d]

165. Isaac and others.[161d] Personal observation. Posner, I.: Sarcoidosis: Case Report, J. Pediatrics **20**:486, 1942.

166. Rosenthal.[71c] Engelbreth-Holm.[161e] Kellert, E.: Miliary Tuberculosis of the Spleen with Thrombopenic Purpura Hemorrhagica, J. A. M. A. **96**:2193 (June 27) 1931.

167. Frank.[69l] Cartwright, G. E.; Chung, H. L., and Chang, A.: Studies on the Pancytopenia of Kala-Azar, Blood **3**:249, 1948.

168. Personal observation. Hirschboeck, J. S.: Hematologic Effects of Splenectomy in Still-Chauffard-Felty Syndrome: A Report of Two Cases, Blood **1**:247, 1946.

169. (*a*) Rosenthal, N.: The Blood Picture in Purpura, J. Lab. & Clin. Med. **13**:303, 1928. (*b*) Jaffe, R. H.: Bone Marrow in Agranulocytosis (Pernicious Leukopenia), Arch. Path. **16**:611 (Nov.) 1933.

nucleosis, recently observed in a boy of 7 years, the platelet count dropped to 66,000. Two days later it rose again to 146,000, but adhesive platelets remained scarce (24,000); bleeding time was somewhat prolonged, and capillary fragility was increased. Transient leukopenia (the count was 1,860) was also present. A reduction is platelet adhesiveness without thrombopenia was also noted in a female patient with chronic brucellosis. Contrary to the general rule, she exhibited virtually no elevation of either platelet count or platelet adhesiveness following an extensive surgical procedure; this may have been another indication of hypersplenism.

Splenic enlargement accompanied with lymphoid hyperplasia, which is characteristic of exophthalmic goiter,[170] possibly explains the tendency to thrombopenia and the excessive tendency to hemorrhage[171] which may prove troublesome during or immediately after thyroidectomy.[171b] Outspoken purpura, however, is rare.[134f] Similar tendencies have been recorded in women during phases of increased estrogenic activity[172] and, in extreme form, probably account for menstrual purpura[172b, d] and menstrual exacerbations of purpura, as well as for purpura occurring during the latter months of pregnancy.[173] These and other endocrine interrelationships with splenic function may be mediated or controlled through the hypophysis.[174] A distinct lowering of platelet adhesiveness was found by us to characterize both hyperthyroidism and pregnancy at term, although in the cases studied the total platelet count was normal or even slightly increased. Platelet tests in a few parturient women showed some variation in the rate of rise of platelet count and

170. Lauda.[86c] Benson, Ott and Scott; Hewitt; Cameron and others; cited by Lauda.[86c]

171. (*a*) Woodruff.[134f] (*b*) Bechgaard, P.: Tendency to Hemorrhage in Thyrotoxicosis, Acta med. Scandinav. **124**:79, 1946.

172. (*a*) Lee and Erickson.[67b] (*b*) Minot, G. R.: Purpura Hemorrhagica with Lymphocytosis: An Acute Type and an Intermittent Menstrual Type, Am. J. M. Sc. **192**:445, 1936. (*c*) Pohle, F. J.: The Blood Platelet Count in Relation to the Menstrual Cycle in Normal Women, ibid. **197**:40, 1939. (*d*) Goldburgh, H. L., and Gouley, B. A.: Postpubertal Menorrhagia and Its Possible Relations to Thrombocytopenic Purpura Hemorrhagica, ibid. **200**:499, 1940.

173. Leschke and Wittkower.[71d] Rosenthal.[169a] Troland and Lee,[87] case 1. Burnett, G. W. F., and Klass, I.: A Review of the Problem of Purpura During Pregnancy, J. Obst. & Gynaec. Brit. Emp. **50**:393, 1943. Finn, W. F.: Thrombocytopenic Purpura in Pregnancy: Review of Literature with Report of Three Cases, Am. J. Obst. & Gynec. **48**:497, 1944.

174. Perla, D.: Relation of the Hypophysis to the Spleen: I. Effect of Hypophysectomy on Growth and Regeneration of Spleen Tissue; II. The Presence of a Spleen-Stimulating Factor in Extracts of Anterior Hypophysis, J. Exper. Med. **63**:599, 1936.

adhesiveness after delivery, but in none was thrombosis diagnosed. Two parturient women exhibited many giant platelets in blood smears taken during the early puerperium.

Action of Thrombocytopen.—The belief that the spleen exerts its physiologic control over platelet number and quality through the agency of a specific hormone, thrombocytopen, has gained increasing acceptance in recent years [175] with the continued accumulation of authoritative data confirming the findings of Troland and Lee [87] (1938). In all published studies, the sole concern has apparently been the effect of relatively crude aqueous extracts containing thrombocytopen on the total platelet count of rabbits and other animals. When one of us (S. E. M.) was also occupied with the problem of the isolation of thrombocytopen from the spleen of purpura hemorrhagica [75] (1944-1945), his attention was likewise directed to the action of thrombocytopen in reducing the platelet count. As an outcome of that study, it was determined that thrombocytopen was of lipid nature and was a product of the normal spleen. The problem of its separation from other splenic lipids was simplified greatly when the existence of its specific biologic antagonist, thrombocytosin, was demonstrated and measures were devised to separate the latter (also a lipid) from the mixture. As mentioned, thrombocytosin is also abundant in adipose tissue, lymph nodes and egg yolk. At that time and subsequently, procedures were developed which made it possible to obtain these substances in a more or less refined state and in suitable amounts for experimental and clinical use. Among the results of these later studies has been the discovery, mentioned previously, that thrombocytopen (usually obtained from bovine spleen) and thrombocytosin (usually obtained from egg yolk) exert their mutually antagonistic influence not only on platelet number but on platelet adhesiveness as well. The effect on adhesiveness was measured by the glass filter method in samples of human or rabbit blood after the oral or parenteral administration of these substances to the living subject or after their addition in high dilution (0.001 per cent) to the citrated specimen of blood in vitro. In rabbits, 5 mg. injections of either substance were regularly effective in producing its specific response. In human patients, significant effects were obtained with doses of 25 to 50 mg., given intramuscularly in aqueous suspension or dissolved in oil. Single doses of 100 mg. of thrombocytopen in human subjects were consistently effective in lowering total platelet count and platelet adhesiveness from high levels to normal levels or slightly below for two to four days; the lowering was generally attended with a slight initial prolongation of

175. Major and Weber (1939); Hobson and Witts (1940); Rose and Boyer (1941); Otenasek and Lee (1941); Paul (1942); Uihlein (1942); Cronkite (1944); cited by Moolten.[75] Dameshek and Dekanes, cited by Dameshek and Miller.[22]

bleeding time. Comparable doses of thrombocytosin in cases of purpura had the opposite effect, raising platelet adhesiveness and, to some extent, total platelet count, and shortening bleeding time, as described.

CONCLUSIONS

The data given in the body of this paper, including the experiences just cited, are believed to justify the following hypotheses regarding the role of the spleen in thrombosis and in hemostasis:

1. By the agency of thrombocytopen, a lipid hormone produced in its reticuloendothelial elements, the spleen normally exerts a moderating influence on the tendency to thrombus formation.

2. This effect depends on the capacity of thrombocytopen to limit the number and adhesive quality of blood platelets and, thereby, to retard the formation and growth of white thrombi.

3. An increased number and adhesiveness of blood platelets and, hence, an increased predisposition to the formation of massive thrombi, result from the action of thrombocytosin, a lipid substance normally present in subcutaneous fat and mobilized therefrom by trauma or lipolytic ferments or absorbed into the circulation as a dietary factor occurring in fatty materials of animal origin.

4. The relatively stable range of the total platelet count and, particularly, of the adhesive platelet count under normal conditions is evidence of an adaptative mechanism which constantly adjusts the functional activity of the spleen in order to protect the organism against the effects of widely fluctuating amounts of thrombocytosin entering the circulation.

It remains a hopeful objective for the future to determine whether or not thrombocytopen can be utilized practicably in the human being for reducing excessive platelet adhesiveness in the prophylaxis of thromboembolism.

SUMMARY

The massing of blood platelets as an adherent plug is the primary event in thrombosis, as it is in the arrest of hemorrhage. Clotting is its sequel and rapidly follows lysis of the accumulated platelets, wherein clot-accelerating factors are liberated. The platelet plug (white thrombus) is the principal means of attachment of the blood clot (red thrombus) until the latter is organized by invading fibroblasts. Clot retraction before organization favors the detachment of emboli.

Endothelial "wettability" and platelet adhesiveness are the principal governing factors in thrombosis. Experiments are described demonstrating relative nonwettability in unopened blood vessels and the progressive development of wettability under conditions which probably favor thrombosis. Analogous conditions probably also exist in arteries damaged by atheroma, prolonged spasm or compression, in veins sub-

jected to angulation, compression or inflammation, and on the intravenous introduction of fat solvents such as ether and alcohol or of detergent agents, including the saponins of crude digitalis. Endocardial vegetations and mural thrombi in the heart may be similarly caused.

An increase in the number and adhesiveness of platelets results from the action of thrombocytosin, a lipid of body fat, which is probably liberated by direct trauma (e. g., surgical incisions, fractures, cutaneous irritations or cellulitis), by proteolytic or lipolytic ferments activated by tissue breakdown of any type (e. g., myocardial infarction, vascular gangrene or carcinoma) or after the ingestion of dietary fat of animal origin. Thrombocytopen, a lipid of the spleen which suppresses platelet formation and adhesiveness, is probably the physiologic antagonist of thrombocytosin.

A new method of measuring platelet adhesiveness to wettable surfaces is described in which citrated blood is filtered through a wick of glass wool; the relative loss of platelets by adsorption is computed as the "adhesive index," from which the proportion of adhesive platelets is calculated. A marked increase in platelet adhesiveness suggests a predisposition to thrombosis, whereas a pronounced decrease in adhesiveness is found in purpura associated with splenic hyperfunction. Platelet adhesiveness is particularly high and persistent in cancer, paralleling an increased tendency to thrombosis. Similar findings occur in polycythemia vera, idiopathic thrombocythemia and related conditions, which probably represent primary disorders of the bone marrow rather than a response to thrombocytosin.

A rapid fall in the platelet count, and particularly in the number of adhesive platelets, from a previously high level often portends the formation of thrombi and aids in their preclinical recognition. Increased coagulability of the blood is probably secondary to the accelerated production of thrombin about white thrombi. Heparin sodium tends to lower platelet adhesiveness and probably retards lysis. Dicumarol® has much less effect. Thrombocytopen causes a fall in the platelet count and adhesiveness and some prolongation of bleeding time; these effects suggest its practical value in the prophylaxis of thrombosis. Thrombocytosin, its antagonist, has been found useful in the therapy of purpura.

Deficient splenic function may be one of the factors which predispose to thrombosis. Conversely, normal splenic function may include protection of the circulatory tree against thrombosis.

CONCEPTS OF MYOCARDIAL ISCHEMIA

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MYOCARDIAL ischemia occurs whenever there exists a discrepancy between the available oxygen supply and the work requirements of the heart muscle. The balance of these two factors is essential for cardiac function. An arterial blood flow below that customarily available for work performance results in myocardial ischemia.

As shown in table 1, a decrease in oxygen supply to the heart muscle may be absolute, owing to narrowing of arterial caliber by occlusive disease, prolonged spasm or a decrease in the oxygen-carrying capacity of the blood (anemia). The decrease may be relative when the arterial supply provided for the normal heart must serve a greater muscular mass than normal (as in cardiac hypertrophy) or when the energy requirements exceed the maximal capacity of the coronary bed. It is also possible that the utilization of available oxygen is impaired either because oxygen is offered to the tissues in nonutilizable form (as in carbon monoxide poisoning) or because certain oxidation systems of the heart muscle cells are paralyzed (as in cyanide poisoning). The failure of oxygen utilization may be responsible for changes in the electrocardiogram observed during these states. It is rarely severe enough to be of clinical significance because irreparable respiratory paralysis occurs before the heart is permanently impaired.

The work of the heart, the second factor in table 1, is customarily divided into useful or external work, visibly expended in the propulsion of blood against peripheral resistance, and internal work, which may be expressed by the total energy liberated minus the external work performed. The ratio of energy liberated to work performed determines the efficiency of the heart muscle. The external work of the heart may be roughly estimated from cardiac output and peripheral resistance. As shown in figure 1, an increase in the work load is invariably associated with an increase in the coronary flow. The injection of large amounts of

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epinephrine into an experimental animal regularly increases the work requirements beyond the capacity of the coronary circulation, and severe myocardial ischemia results. The administration of epinephrine has been proposed as one of the tests for the efficiency of the coronary circulation in man, in whom a similar reaction, though a less severe one, may be induced. It is doubtful, however, that in subjects with an adequate blood supply to the heart muscle and in the absence of external stimulation with epinephrine the cardiac work load can be increased out of proportion to the available reserves of the coronary bed, although this inference has been made from time to time. On the other hand, a comparatively slight decrease in oxygen supply or oxygen utilization, which may be induced by a variety of etiologic factors, may be enough to induce myocardial ischemia in an apparently normal heart when cardiac work is increased due to any of the factors mentioned in table 1. Furthermore,

TABLE 1.—*Causes of Myocardial Ischemia*

Cause	Condition
Decrease in oxygen supply	
Absolute	Disease of the coronary arteries; anemia
Relative	Cardiac hypertrophy; excessive external and internal work
"Chemical" (enzymatic?)	Failure of utilization
Increase in work requirement	
Due to increased heart rate	
Due to increased input and output load	Increased volume flow and increased peripheral resistance
Due to decreased efficiency	Structural defects; "chemical" factors

the heart is not an efficient organ: Only about 10 per cent of the available energy is expended as external work.[1] Without apparent changes in the work load of the heart, myocardial ischemia may develop if the efficiency decreases as the result of valvular defects or of poorly understood chemical (enzymatic?) processes preceding the onset of congestive heart failure. In this case, for a given task a greater than normal effort is needed, and the signs of ischemia may appear though the apparent work load is unaltered or actually decreased and the oxygen supply unchanged.

In figure 1, the physiologic imbalance responsible for the signs and symptoms of myocardial ischemia is indicated. As soon as a "point of tolerance" is reached, the limits of the available reserves are exceeded and myocardial ischemia ensues. When the blood supply to the working organ decreases below this point, a state of "coronary insufficiency" results. The term "myocardial ischemia" is preferred because it defines

1. Landowne, M., and Katz, L. N.: Heart: Work and Failure, in Glasser, O.: Medical Physics, Chicago, The Year Book Publishers, Inc., 1944, p. 578. (Includes further references.)

more clearly the functional alterations that take place. It is, of course, admitted that diseases of the coronary arteries constitute by far the commonest cause of myocardial ischemia. The syndrome occurs, however, without obvious anatomic alteration of the arteries themselves. It is not infrequently seen in the wake of severe infections, including diphtheria, or as the result of sensitivity reactions (serum sickness, rheumatic fever, streptococcic states). The mechanism by which oxygen supply and oxygen utilization are involved in such processes has not been elucidated in all instances. Indeed, an almost infinite variety of abnormal states and combinations of reactions may lead to the syndrome. Certain anatomic aspects of it have been discussed from time to time. The subendocardial location of the anatomic manifestations has usually been stressed.[2] As will be shown, there is strong electrocardiographic evidence that these may not be the only regions involved.

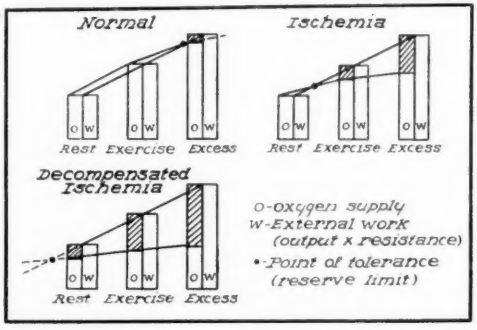

Fig. 1.—Discrepancy between oxygen supply and external work performance. An increase in internal work performed (change in metabolic requirements) may cause ischemia though external effort remains unaltered. Note that in progressive ischemia the point of tolerance is shifted to the left of the diagram.

It is obvious from the diagram that the determination of the point of tolerance—the limit of the available reserves—is of importance in the evaluation of the patient's condition. It is equally apparent that this determination requires that the patient be examined while subjected to increasing work loads (exercise), as signs and symptoms of the syndrome appear at rest only in decompensated severe myocardial ischemia.

2. (*a*) Buchner, F.: Die Koronarinsuffizienz, Dresden, Steinkopff, 1939. (*b*) Master, A. M.; Dack, S.; Grishman, A.; Field, L. E., and Horn, H.: Acute Coronary Insufficiency: An Entity, J. Mount Sinai Hosp. **14**:8, 1947. (*c*) Master, A. M.: Acute Coronary Diseases, Am. J. Med. **2**:501, 1947. (Includes further references.)

CLINICAL AND ELECTROCARDIOGRAPHIC SIGNS

The clinical signs of this state should not be confused with those denoting diseases of the coronary arteries, although, of course, a good deal of overlapping exists. Table 2 indicates that the disorder under discussion is only one of the many manifestations of disease of the coronary arteries. It is admitted that ischemia may be the exciting factor in all, but conduction defects, cardiac irregularities and congestive heart failure obviously are of no value in gaging the presence or the intensity of the syndrome as they may appear from a variety of other causes.

Myocardial ischemia gives rise to two cardinal manifestations regardless of whether an anatomic lesion can or cannot be demonstrated: pain, and changes in the electrocardiogram (table 3).

TABLE 2.—*Clinical Manifestations of Disease of the Coronary Arteries*

None
Conduction defects
Cardiac irregularities
Congestive heart failure
Myocardial ischemia

TABLE 3.—*Clinical Manifestations of Myocardial Ischemia*

When few, if any, detectable anatomic lesions are present
Precordial pain
Electrocardiographic changes
When tissue destruction and repair are present
Precordial pain
Electrocardiographic changes
Physical findings
(Remote reactions [abnormal responses to laboratory tests] may occur)

Pain.—This symptom constitutes the most important guide to the syndrome, but myocardial ischemia may be present without pain, and pain may arise from the myocardium in the absence of ischemia. Moreover, any visceral pain may be changed in intensity and character during its passage over afferent nerve fibers and is profoundly modulated at subcortical and cortical levels. If precordial pain is present it may signal myocardial ischemia, but it is of little value in the evaluation of the severity of the syndrome. Severe ischemia may be induced rapidly without the occurrence of pain. This is indicated by the observation that in 162 anoxia tests performed on 97 patients with myocardial ischemia, pain did not occur in 84 instances, or 50 per cent (table 6).

Electrocardiographic Changes.—The second sign (table 3) appears far more reliable. A change in the pattern of the electrocardiogram may be taken as a sensitive and objective indicator. The value of the electro-

cardiographic examination may be enhanced if a complete selective exploration of various sections of cardiac muscle is carried out by a number of precordial, esophageal and unipolar limb leads. In the series mentioned, 90 per cent of the positive responses were associated with demonstrable electrocardiographic changes. Unless injury to tissue is excessive and has resulted in gross myocardial necrosis the alterations involve only the final portions of the ventricular electrocardiogram, namely, the RS-T segment and the T wave. These depend on (*a*) the degree of ischemia, (*b*) the location of the ischemic region and (c) the preexisting nutritional state of the myocardium. Figure 2 reveals that electrocardiograms obtained from a region subjected to mild ischemia are characterized by inversion of the terminal portion of the T wave or by accentuation of a previously inverted T wave (stage 1), and those indicating severer grades (injury), by elevation of the RS-T segment (stage 2). If the surface of the heart is damaged or if ischemia involves primarily the subepicardial region the electrocardiographic changes will be transmitted directly to the precordium and to other regions to which the effects of electrical excitation of epicardial layers are being transmitted, particularly to the left arm and to the left leg. If endocardial regions primarily are involved, changes in the RS-T segment and the T wave will be transmitted unchanged only to the right arm or to an electrode placed high in the esophagus. However, endocardial ischemia exerts a remote effect on the variations in electrical potential recorded by a precordial electrode or an electrode placed over the left arm or the left leg. These changes will be less intense than, and opposite in sign to, those recorded by an electrode placed in the vicinity of the endocardium. Consequently, in chest leads, and to a certain extent in standard leads, subepicardial ischemia is signaled by inversion of the T wave and elevation of the RS-T segment and an endocardial lesion by an upright T wave and by depression of the RS-T segment. Figure 2 illustrates the various combinations that may be encountered when one region is more intensely involved than the other.

The electrocardiogram of an ischemic region changes because the rate at which the area returns to the resting stage is prolonged (repolarization delay—stage 1 in figure 2). In the severer stages, the heart muscle of this region is electrically never completely at rest (flow of resting currents—stage 2 in figure 2). Uniform ischemia of all muscle layers or ischemia localized to regions deeply embedded in, and surrounded by, well functioning muscle will result in few, if any, electrocardiographic changes; it constitutes the ultimate limitation in electrocardiographic examinations. These considerations may explain the reported instances of myocardial infarction with apparently normal

electrocardiograms,[3] although almost all instances on record lack a complete electrocardiographic work-up.

The intensity of the abnormal reaction and the location of the area that is primarily involved mold the T wave of the electrocardiogram. This concept has found confirmation in many experimental animals and in human subjects exposed to various experimental procedures, and it may be substantiated on clinical grounds. It is possible, therefore,

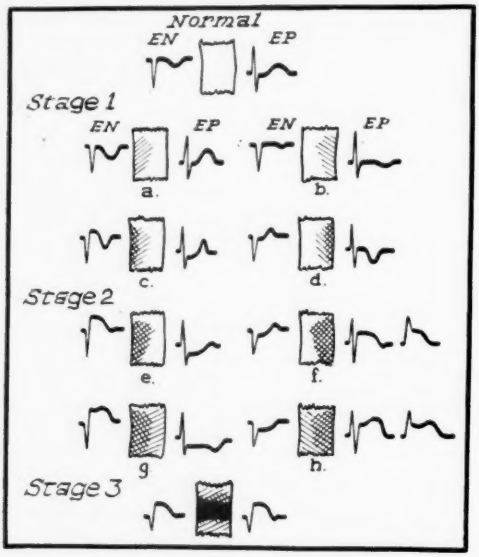

Fig. 2.—Changes in the RS-T segment and T wave in myocardial ischemia. A section of the heart muscle is shown with the endocardial surface (EN: V_R, VE_{30-40}) facing to the left and the epicardial surface (EP: $V_1 - V_6$, V_L, V_F, VE_{45-60}) to the right. Predominantly subendocardial ischemia is illustrated in the left column and predominantly subepicardial ischemia in the right column; the intensity of the process is indicated by hatching and cross hatching. Note that the epicardial electrocardiogram of endocardial injury (*e*), generally described as the pattern of "coronary insufficiency," presents only one of the many possibilities; *g* (subendocardial injury with subepicardial ischemia) yields a pattern that may simulate ventricular enlargement ("strain"). Stage 1 represents myocardial "ischemia" of Bayley (repolarization delay), stage 2 myocardial "injury" of Bayley (incomplete repolarization) and stage 3 myocardial ischemia with obvious destruction of tissue (infarction).

3. Langendorf, R., and Kovitz, B.: Acute Myocardial Infarction Without Deviation of the ST Segment in the Electrocardiogram, Am. J. M. Sc. **204**:239, 1942. Pirani, C. L., and Schlichter, J. G.: Subendocardial Myocardial Infarct, Ann. Int. Med. **25**:847, 1946.

to expand the interpretation of figure 2 into an attempt to explain changes in the T wave in general.

This approach implies that many types of changes in the T wave may result from myocardial ischemia. "Coronary insufficiency" has usually been described as resulting in flattening of the T wave and in depression of the RS-T segment.[2] Such a statement is incomplete, as it describes only the epicardial pattern of severe endocardial ischemia (fig. 2, stage 2, muscle strip on the left). It is also true, however, that this pattern is frequently seen in conditions associated with myocardial ischemia. One must conclude that the endocardial surfaces are more vulnerable than other sections of cardiac muscle, a well known fact that has recently been confirmed again by experiments with the infusion of fluorescein sodium.[4]

Induced anoxemia or spontaneously occurring myocardial ischemia may reveal any of the types of changes in the S-T segment and the T wave in figure 2.[5] Terminal inversion of the T wave without displacement of the R-T segment, apparently signalling predominant subepicardial ischemia, may occur in cases of hypertrophy of the left ventricle. Typical examples of this kind of change in the T wave are indicated in figures 3 and 4 and should be contrasted with the pattern of "coronary insufficiency" of Master and others.[2b,c]

Long-standing severe ischemia or sudden temporary cessation of the blood supply to one area may lead to necrosis of muscular tissue, which is best seen in true myocardial infarction secondary to occlusion of a coronary artery. When such destruction of tissue occurs, a number of new signs appear. The electrocardiogram reveals, in addition to the changes of ischemia, a sharp reduction in the R wave of the QRS complex with the appearance of the Q waves in regions dominated by epicardial effects. An epicardial lead then resembles a lead taken from the cavities (stage 3, fig. 2), because the endocardium and the epicardium are separated by a layer of nonfunctioning (necrotic) tissue which does not become involved in the process of activation. The complex electrocardiographic picture of myocardial infarction with (*a*) an excessively deep Q wave, (*b*) elevation of the RS-T segment and (*c*) changes in the terminal portion of the T wave resolves itself readily into evidence of necrosis and scarring, severe injury and milder states of ischemia (fig. 5). These patterns may be recorded in succession when in

4. Prinzmetal, M.; Bergman, H. C.; Kruger, H. E.; Schwartz, L. L.; Simkin, B., and Sobin, S. S.: Studies on the Coronary Circulation: III. Collateral Circulation of Beating Human and Dog Hearts with Coronary Occlusion, Am. Heart J. **35**:689, 1948.

5. Hecht, H. H.; Abildskov, J.; Bolin, R., and Focht, F. S.: Observations on the Human Heart During Induced Hypoxia (the Ischemia-Injury Pattern), Am. J. Med. **4**:623, 1948.

experimentally induced infarction an electrode is moved from the center of the infarct toward the periphery.[6] They may be seen in patients examined by serial precordial leads, and in whom the inversion of the T wave (a sign of mild ischemia surrounding the infarcted region) is usually observed over a larger area than is elevation of the RS-T segment and the Q wave. They explain the succession of electrocardiographic changes over a period of time in patients recovering from such an episode. Figure 6 illustrates the changes that occur in time and space in patients with myocardial infarction. With the exception of Q waves which usually though not always indicate transmural necrosis, the

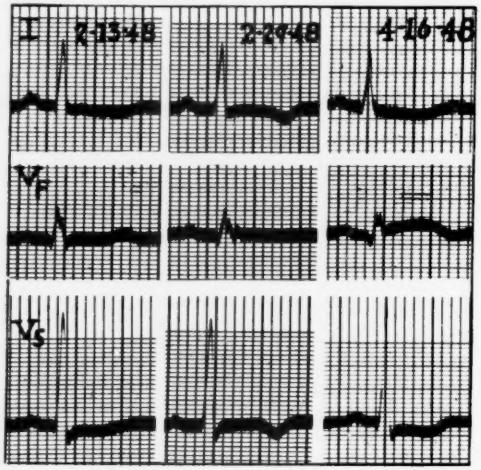

Fig. 3.—Myocardial ischemia with and without destruction of tissue, illustrated by electrocardiograms in the case of a male laborer of 55 with hypertensive heart disease associated with angina pectoris. All leads were taken on each occasion. Leads I, V_F and V_5, made on Feb. 13, 1948, revealed flat T waves with depression of the RT segment when the patient was at rest ("subendocardial ischemia"). On February 29, the RS-T segment was normal, but terminal inversion of the T wave was noted ("subepicardial ischemia"). On April 16, posterior myocardial infarction occurred (transmural necrosis with "injury" effects—stage 3 in fig. 2); leads I and V_5 were then similar to the first record. Changes of this type may represent remote effects of the infarction or may indicate additional myocardial ischemia of the anterior endocardial surface of the left ventricle.

changes are reversible. If a patient in whom only changes in the T wave remain from a previous episode of infarction is again subjected to the

6. Wilson, F. N.; Johnston, F. D., and Hill, I. G.: The Form of the Electrocardiogram in Experimental Myocardial Infarction: IV. Additional Observations on the Later Effects Produced by Ligation of the Anterior Descending Branch of the Left Coronary Artery, Am. Heart J. **10**:1025, 1935.

insult of ischemia, the pattern will revert to that of a more acute phase (fig. 8). It is obvious that such behavior is of prognostic value.[5]

The other changes noted in table 3 are related also to the destruction of body tissue and to the intense inflammatory and regenerative reactions that follow. A sharp reduction in the intensity of the first heart sound, often associated with an early diastolic apical gallop rhythm, is commonly noted. Pulsus alternans may be present. If work performance decreases as the result of the injury, the blood pressure falls and the intensity of the second sound likewise diminishes. Fluoroscopic, kymographic and electrokymographic examinations may reveal changes in the cardiac contour with local diminution of cardiac contraction, particularly when the infarcted area involves the lateral cardiac surface

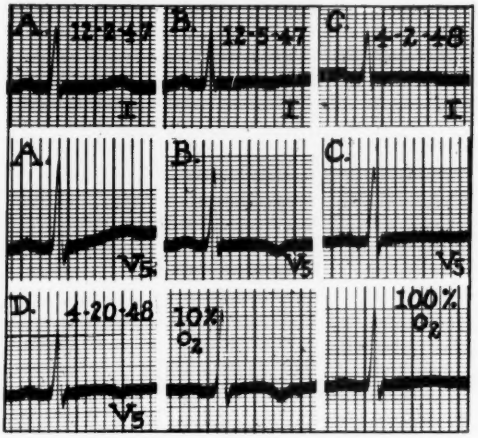

Fig. 4.—Myocardial ischemia without tissue destruction of the subepicardial type, illustrated by electrocardiograms in the case of a male office worker of 52 with hypertensive heart disease and frequent anginal attacks.

On Dec. 2, 1947, an essentially normal record was obtained (*A*). On December 5 (*B*), the T wave appeared flat in lead I and showed terminal inversion in lead V_5, as indicated in *g*, figure 2. On April 2, 1948 (*C*) the record resembled that in *A*. During an anoxia test performed a few days later (*D*), the T wave temporarily reverted to the pattern of *B*, demonstrating that the changes in *B* were apparently caused by myocardial ischemia, presumably of the subepicardial type. The spontaneous changes occurred many times, and the response to the anoxemia test was repeated frequently. Note that no shift in the RS-T segment occurred at any time.

or when the heart is horizontally placed. The intense regenerative reactions result in fever and leukocytosis a few days after the insult. Some associated changes, such as the rise in the sedimenation rate, the temporary increase in the excretion of urobilinogen in the urine,

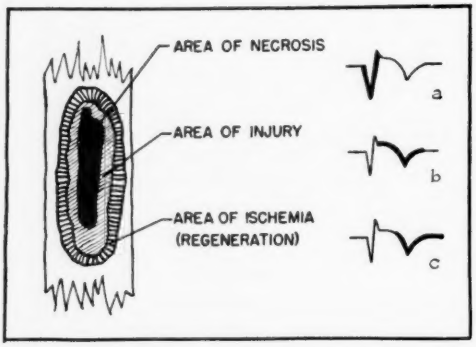

Fig. 5.—Origin of the components of the electrocardiogram (further explanation in text). The central area of necrosis, an electrically inert region, permits the escape of the potential variation of the endocardium to the surface. As these are primarily negative in an otherwise normally activated heart, deep Q waves occur in surface leads (*a*). The central region is surrounded by an area that is severely anoxic ("injury") and may or may not be incorporated into the final inert fibrotic scar. As long as this region remains in the injured stage it becomes incompletely depolarized during diastole, which for reasons beyond the scope of this presentation results in elevation of the RS-T segment (*b*). The outer shell of the infarcted region is less intensely involved. Moderate anoxia of tissue causes a certain delay of repolarization which in leads dominated by this region results in inversion of the terminal portion of the T wave (*c*). The division is arbitrary and changes with time (fig. 6).

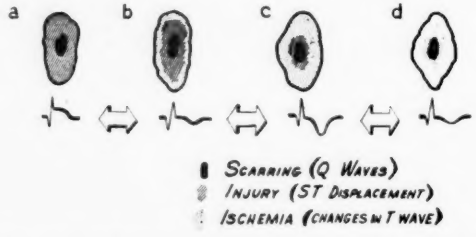

Fig. 6.—The pattern of myocardial infarction; sequential changes in time and space. The reversible changes of the S-T segment and the T wave may be correlated with the intensity of the ischemia present. As healing progresses the area surrounding the central necrotic region returns to a functional state that approaches the normal (shift from *a* to *d*). Additional injury (induced anoxia) may cause a reversal to the acute phase if collateral circulation has not been adequately established (shift from *d* to *a*, as shown in figure 8). Solid black indicates necrosis; hatching, severe ischemia ("injury"), and stippling, mild marginal ischemia.

hyperglycemia, glycosuria and certain changes in the protein pattern, may perhaps be regarded as secondary to mild impairment of liver function rather than viewed as a direct result of tissue breakdown.

In table 4, the signs of tissue injury are contrasted with those denoting tissue destruction. The subdivision of myocardial ischemia into these two groups has certain advantages over the time-honored division into "angina pectoris," a clinical syndrome, and "coronary occlusion," a pathologic entity. There are intermediate states in which an exact division appears impossible on clinical grounds. A reasonably definite estimate of the functional impairment that has resulted can usually be made if the signs of tissue destruction are contrasted with those denoting injury.

The term "ischemia" [stage 1, fig. 2] and "injury" [stage 2, fig. 2] are used in a quantitative sense, as in the experiments of Bayley, LaDue and York.[7] They demonstrated that the various types

TABLE 4.—*Signs of Injury and Destruction of Tissue*

Tissue Injury	
	Pain
	Changes in terminal portion of T wave ("ischemia")
	Displacement of RT junction ("injury")
Tissue Destruction	
	Increase in body temperature, white cell count, sedimentation rate, excretion of urobilinogen
	Decreased R waves; excessive Q waves

of electrocardiographic changes described by many previous observers are a function of the intensity of the ischemia induced. There is little doubt that this is true for the human heart as well.[8] If the term "ischemia" is replaced by "repolarization delay" and "injury" by "flow of resting current" or "incomplete repolarization," the concept may be applied to changes in the T wave in general.[9])

7. Bayley, R. H.; LaDue, J. S., and York, D. J.: Electrocardiographic Changes (Local Ventricular Ischemia and Injury) Produced in the Dog by Temporary Occlusion of a Coronary Artery, Showing a New Stage in the Evolution of Myocardial Infarction, Am. Heart J. **27**:164, 1944.

8. Hecht and others.[5] Johnston, F. D., and Wilson, F. N.: Electrocardiographic Findings in the Presence of Myocardial Injury, Mod. Concepts Cardiovas. Dis. **16**: (n. p.) (June) 1947. Bayley, R. H.: An Interpretation of the Injury and the Ischemic Effects of Myocardial Infarction in Accordance with the Laws which Determine the Flow of Electric Currents in Homogenous Volume Conductors, and in Accordance with Relevant Pathologic Changes, Am. Heart J. **24**:514, 1942.

9. Hecht, H. H.: On Changes of the T Wave and the RST Segment of the Human Electrocardiogram, Am. Heart J. **37**: 639, 1949.

FUNCTIONAL TESTS

It was stated that myocardial ischemia may be detected at rest only when present in advanced degree. For an objective determination of the "point of tolerance" it is necessary either to decrease the oxygen supply still further or to increase the work performance (table 5). Functional tests devised with this in mind are not without danger, as the point of tolerance should be approached but must not be exceeded. All these tests have the same end point: the production of electrocardiographic changes

TABLE 5.—*Experimental Induction of Myocardial Ischemia*

By decrease in oxygen supply	
	Anoxic anoxemia
	Reflex spasm of coronary arteries (due to cold)
By increase in work requirements	
	Exercise
	Administration of epinephrine

TABLE 6.—*Results of 200 Anoxia Tests Performed on 131 Patients*

Diagnosis	Number of Tests	Number of Patients	Result of Test, Percentage of Tests Performed: Pain and Electrocardiographic Changes	Electrocardiographic Changes	Pain	No Response
Patient normal	21	21	0	0	0	100
Neurosis (neurocirculatory asthenia)	17	13	0	12	53	35
Myocardial ischemia without tissue destruction (angina pectoris)	94	50	44	31	10	9
Myocardial ischemia with tissue destruction (myocardial infarction)	68	47	28	38	9	25
Totals	200	131	30	30	12 (10.5*)	17†

* Percentage of tests resulting in pain in examples of myocardial ischemia.
† Percentage of tests resulting in last three diagnoses only.

or (much less reliable) the onset of precordial pain or its equivalent. Increase in work performance is difficult to grade and hard to control. An oxygen debt may occur if the point of tolerance is inadvertently exceeded. This cannot be corrected immediately if the patient exercises or if epinephrine has been injected. After some hesitation we have chosen to decrease the arterial oxygen supply artificially by the inhalation of a mixture of 10 per cent oxygen in nitrogen (87 per cent) and carbon dioxide (3 per cent). As oxygen saturation decreases very rapidly during the first five minutes and then remains relatively constant, definite evidence of myocardial ischemia is usually obtained during the first ten minutes of the test. It is never carried over twenty minutes. If the

test is modified from the original description by Levy and others [10] to include a number of unipolar limb leads and precordial leads and if the test is evaluated in accordance with the patterns illustrated in figure 2 rather than by using arbitrary standards, a great deal of information may be obtained.[6] The experimental procedure allows the subject to be outwardly at rest in the recumbent position, which greatly facilitates the study of such patients. It permits instantaneous administration of 100 per cent oxygen as soon as the point of tolerance is reached. No oxygen debt is encountered, and the lowered arterial oxygen saturation, which in Salt Lake City amounts to 75 per cent of normal, is corrected within one minute. The addition of carbon dioxide eliminates many objections that have recently been raised by tending to establish a uniform respiratory rate and depth. No lasting adverse reactions were encountered in over 300 tests, two thirds of which were performed on patients with myocardial ischemia with and without destruction of tissue. Table 6 gives the over-all results of the test in the first 200 instances; table 7

TABLE 7.—*Practical Value of the Anoxia Test*

Differential diagnosis of precordial pain
Estimation of "point of tolerance"
Estimation of rate of recovery (prognosis)
Estimation of therapeutic procedures

illustrates how such a functional approach may be of value in evaluation of the diagnosis, therapy and prognosis of myocardial ischemia.

PROGNOSIS

From the clinical course in cases of advanced degrees of myocardial ischemia, and by the use of a functional approach only, as outlined, it became apparent that the prognosis in such cases does not depend on the location or the severity of the original insult but on (*a*) the size and penetrance of the lesion and (*b*) the speed and efficiency with which collateral circulation develops. In severe ischemia with or without destruction of tissue, the size of the lesion can be estimated from the number of precordial and esophageal leads involved in the process. When the changes are confined to the R-T segment and the T wave but other signs pointing to destruction of tissue are noted, nonpenetrating myocardial infarction may be present. Such infarcts are benign when they involve the epicardial surface; they are almost always fatal when they spread endocardially. In general, of course, the more severe the degree of ischemia and the more extensive the involvement of the heart

10. Levy, R. L.; Williams, N. E.; Bruenn, H. G., and Carr, H. A.: The "Anoxemia Test" in the Diagnosis of Coronary Insufficiency, Am. Heart J. **21**:634, 1941.

muscle in the process, as estimated from the electrocardiogram, the poorer the outlook; yet, there are significant exceptions. There are patients who display severe ischemia with injury, as demonstrated by upward displacement of the R–T junction, continuously for months and years. An extreme example of this kind is illustrated in figure 7. In this case, severe myocardial ischemia of the "injury" type (stage 2, fig. 2) was present over a four year period. Katz described similar instances.[11] The changes in such patients depend on the presence of a severely ischemic region which fails to improve but is also not converted into inactive scar tissue. Such records are usually the result of extreme

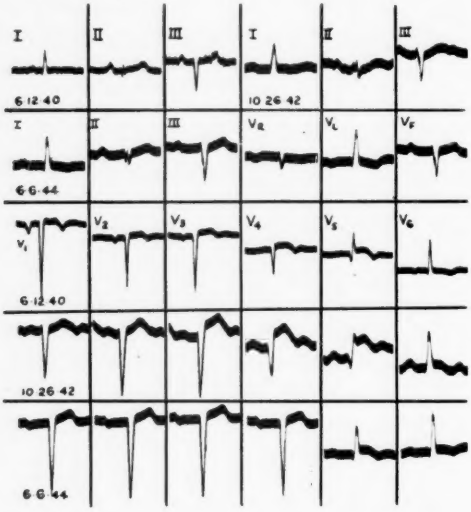

Fig. 7.—Unretouched tracings (time lines omitted by overexposure) showing prolonged myocardial injury with permanent elevation of the S-T segment in the case of a female infirmary inmate of 65 with frequent attacks of angina pectoris. Precordial leads taken over a four year interval regularly display a pattern suggestive of "recent" myocardial infarction. It is assumed that inadequate collateral circulation arrested the usual electrocardiographic evolution at stage *b* of figure 6. Similar cases of much shorter duration were reported by Katz [11] and Wilson and others (Am. Heart J. **27**:62 [fig. 25], 1944).

ischemia caused by an almost complete occlusion of a coronary artery with a pinpoint lumen. A trickle of blood rinsing such regions apparently interferes with the development of an adequate collateral circula-

11. Katz, L. N.: Electrocardiography, ed. 2, Philadelphia, Lea & Febiger, 1946, p. 369.

tion. If, on the other hand, in subjects recovering from the effects of myocardial infarction the pattern of the electrocardiogram as illustrated in figure 6 reverts from stage *d* to stage *b*, it is assumed that new injury has occurred or that an extension of the infarcted region has taken place. If it occurs spontaneously it must be regarded as an ominous sign. It may be experimentally induced in patients who have recovered and are subjected to an anoxia test. The temporary reversal during induced hypoxia twenty-five days after an episode of myocardial infarction in a woman of 69 is illustrated in figure 8. The reappearance of the pattern of acute injury during the test indicates that an adequate collateral circulation has not been fully developed. In such patients, the point of tolerance is, therefore, easily exceeded, and the activities of subjects displaying such a reaction should be severely restricted. In other cases, no changes occur during the test, as early as one month after the original insult. It may be assumed that adequate collateral circulation has been established. It is suggested that such a functional approach may be of help in the evaluation of the disorders and in the rehabilitation of sub-

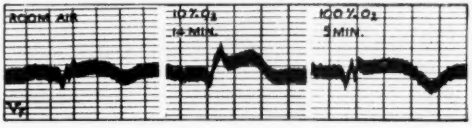

Fig. 8.—Response to induce anoxia in myocardial infarction in the case of a housewife of 69. Myocardial infarction occurred four weeks prior to the anoxia test. No pain was signaled, but the response reverted from stage *d* to stage *b* of figure 6, suggesting incomplete revascularization of the area surrounding the infarct. (Only lead V_F is reproduced).

jects who have suffered from one or more episodes of myocardial infarction. It is for this reason that the anoxia test has become a standard procedure in our patients with myocardial infarction on discharge from the hospital and at regular periods thereafter. In some instances, we have found that the original ischemic area remained unchanged during the test but that areas remote from the original site responded with an ischemic pattern. This response may point to the existence of additional regions with impaired blood supply. The prognosis should be guarded for such patients and their activity restricted.

It is fortunate that even in a normal heart an abundant collateral circulation exists. It remains dormant until a sudden obstruction of a major pathway permits the opening of preformed collateral channels.[4] A gradual reduction in arterial blood supply is apparently a much less efficient stimulus than sudden cessation of flow. Consequently, some patients with myocardial ischemia with destruction of tissue appear to tolerate the effects of anoxia better than subjects who suffer from

ischemia without destruction. This clinical impression is supported by the observation that 25 per cent of the patients for whom the test was performed from a few weeks to a few months after the infarction showed neither electrocardiographic nor subjective evidence of further impairment during the test, while this was true of only 9 per cent of patients with apparent ischemia but without infarction (table 6).

The importance of an adequate collateral circulation is demonstrated by 2 examples (fig. 9). In both cases, complete occlusion of the descending branch of the left coronary artery was demonstrated at autopsy. A

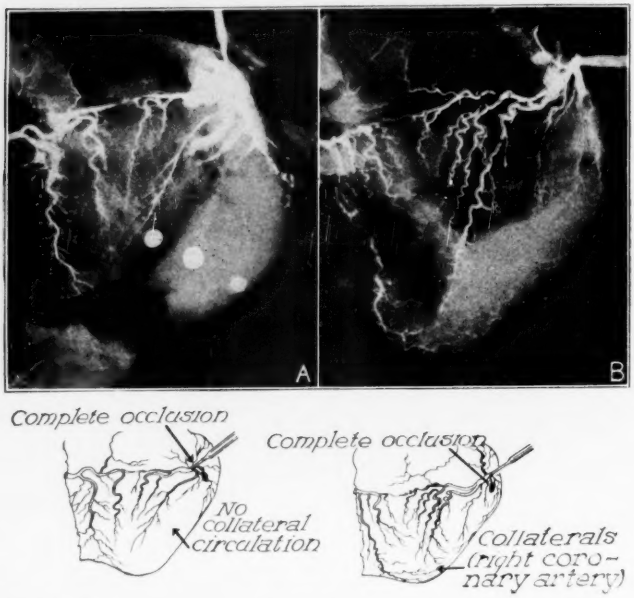

Fig. 9.—Spontaneous revascularization in myocardial infarction. Two examples of complete occlusion of the anterior descending branch of the left coronary artery are compared (further explanation in text). The hearts were injected and dissected according to the method of Schlesinger. In *B*, all visible vessels beyond the point of occlusion were filled by the injection mass introduced into the right coronary artery, showing adequate collateral circulation. The right ventricle filled normally in both cases (compare with Blumgart, H. L.; Schlesinger, M. J., and Davis, D.: Am. Heart J. **19**:1, 1940).

The white dots in *A* represent, from right to left, the positions for precordial leads V_4, V_5 and V_6.

woman of 76 (fig. 9*B*) survived the insult and succumbed many years later to lobar pneumonia. The other patient, a man of 56 (fig. 9*A*), died in heart failure three weeks after the attack. It can be seen clearly

that in the first patient adequate filling of the region usually supplied by the left coronary artery had been accomplished from the opposite side. The heart was functionally competent, and with the exception of a scar the effect of the ischemia had been completely overcome. In the second case, compensatory adjustments failed and a large, completely ischemic region involving major portions of the left ventricle led to intractable heart failure and to death. It is clear that a functional test from which conclusions may be drawn regarding the adequacy of the collateral circulation following a major attack of ischemia should prove to be a valuable tool in the guidance of such patients.

TREATMENT

In the first case (fig. 9*B*), no specific treatment was instituted. In fact, the attack was not recognized; yet, a functionally adequate result

TABLE 8.—*Treatment of Myocardial Ischemia*

Increase in oxygen supply
Administration of oxygen
Administration of nitrites
Parenteral administration of aminophylline
Administration of alcohol (large doses of papaverine [?] and possibly of khellin)
Correction of underlying associated diseases
Decrease in work performance
Sedation
Relaxation
Active decrease in metabolism

ensued. Minor degrees of ischemia secondary to changes other than those occasioned by diseases of the coronary arteries usually are relieved on recovery from the initiating process. As demonstrated, complete occlusion of a coronary artery is also not infrequently followed by adequate functional recovery. It is less well recognized that patients with ischemia due to narrowing of the coronary arteries (or with angina pectoris) in the main also improve spontaneously or on the institution of a few simple measures (table 8). Unless carried out over long periods of time, the evaluation of agents alleged to cure angina pectoris is extremely difficult. At present, it may be said that quick-acting vasodilators are certainly beneficial in the acute attack. Unless they decrease peripheral resistance precipitously, they tend to increase the oxygen supply to the heart muscle. If they are frequently taken and if at the same time the work requirements of the heart muscle are reduced by sedation, purposeful rest or, in an occasional case, by decreasing metabolic requirements with thiouracil derivatives, the discrepancy between oxygen supply and work requirements may be overcome and the patient restored to a useful life.

There are no agents or practical procedures, however, that will consistently promote collateral circulation, increase oxygen uptake of the heart or otherwise correct the results of the discrepancy between oxygen supply and work requirements. It is significant that when such substances are introduced it is stated that treatment is to be continued for months at a time. During such prolonged periods of observation spontaneous improvement is likely to be observed, particularly if the patient has been instructed carefully to record the frequency of his attacks and the number of glyceryl trinitrate tablets consumed. This leads the patient to discover the factors in exceeding the point of tolerance which cause an increased demand for vasodilators. Such efforts will be consciously or unconsciously avoided. If it is insisted that no treatment other than mild sedation and the administration of glyceryl trinitrate be instituted for several months before the patient is placed on a new form of treatment, and if the patient is asked to chart his course carefully, spontaneous "improvement" is the rule rather than the exception. In spite of apparent improvement, in some cases the response to the anoxia test remains unaltered over the years. This implies that in these subjects collateral circulation has not appreciably increased but that the patient has learned to reduce his activity to below the point of tolerance. In other examples, actual improvement may be demonstrated by the patients' increased tolerance to artificially induced hypoxia. In either case, it may be said that myocardial ischemia shows an inherent tendency to spontaneous improvement in the majority of patients who adjust their activities to their disease.

SUMMARY

1. Many factors upset the balance between oxygen supply and work requirements of the heart muscle. This results in general or local myocardial ischemia. Diseases of the coronary arteries are the most important but not the only factors leading to the appearance of the syndrome.

2. The syndrome of myocardial ischemia is characterized by pain, electrocardiographic changes and certain remote reactions secondary to tissue destruction. Pain is an unreliable guide. The electrocardiographic changes are manifold and in the less severe stages involve only the S–T segment and the T wave. They are determined by the intensity of the process and by the location of the lesion with respect to the recording electrodes. "Delay of repolarization" involves the T wave proper; "incomplete repolarization" (with flow of resting currents during diastole) modifies the RS-T segment. The direction of the changes with respect to the isoelectric base line of the electracardiogram is determined by the location of the predominantly ischemic region. "Subendocardial" and "subepicardial" involvement may thus be contrasted.

3. In myocardial infarction, the signs of gross tissue destruction are added to those of myocardial ischemia. It is therefore suggested that the term "myocardial ischemia without tissue destruction" be used to define angina pectoris and "myocardial ischemia with tissue destruction" to denote myocardial infarction. The new terms allow an estimation of the functional impairment of intermediate clinical states in which the diagnosis of "severe angina pectoris" or "coronary occlusion" cannot be made with certainty.

4. The "point of tolerance" defines the limits of cardiac reserve. In decompensated ischemia, the signs and symptoms appear when the patient is at rest. If an appreciable cardiac reserve is still available, an objective diagnosis can only be made by appropriate functional tests. The inhalation of a mixture of a small amount of oxygen with nitrogen and carbon dioxide in conjunction with a detailed electrocardiographic examination is suggested as a useful and relatively harmless procedure.

5. Alterations in the electrocardiogram during the test in patients who have suffered an episode of myocardial infarction depend largely on the degree of revascularization. The result of the test in such patients may allow certain limited prognostic conclusions.

6. Myocardial ischemia from any cause tends to improve spontaneously in many instances. Under palliative treatment, the majority of patients may be returned to a useful life once they have learned to adjust their activities to their limitations.

EXCRETION OF CHOLINE IN THE URINE OF DIABETIC PATIENTS

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THE IMPORTANCE of choline as a dietary factor was first detected in depancreatized dogs which were given insulin over a long period. It was found that choline was able to inhibit the development of fatty liver in such animals.[1] Later it was shown that choline is generally an essential dietary factor, playing an important role in fat metabolism.[2] As diabetes mellitus represents a disease with disturbances not only in the carbohydrate metabolism but also changes in the fat and protein metabolisms, it can be assumed that in this case also the choline plays some part after acting as a general regulator in the fat metabolism. It was shown by Conte-Marotta [3] that choline given orally in large dosage is able to decrease the rate of development of ketone bodies in white rats with phlorhizin diabetes. Paul, Daum and Kemp,[4] on the other hand, were able to show that hyperlipemia in diabetes mellitus disappears after administration of choline. Pelner, Davidson, Waldman and Margolis [5] reported that 18 diabetic patients were successfully treated with choline, whereas 8 did not respond to the medication.

From the Department of Metabolic Research, Wenner-Grens Institut, Stockholms Högskola.

1. Best, C. H.; Ferguson, G. C., and Hershey, J. M.: Choline and Liver Fat in Diabetic Dogs, J. Physiol. **79**:94-102, 1933.

2. (*a*) Best, C. H., and Lucas, C. C.: Choline—Chemistry and Significance as a Dietary Factor, in Harris, R. S., and Thimann, K. V.: Vitamins and Hormones: Advances in Research and Applications, New York, Academic Press, Inc., 1943, vol. 1, pp. 1-58. (*b*) Jukes, T. H.: Choline, Ann. Rev. Biochem. **16**:193-222, 1947.

3. Conte-Marotta, R.: Influenza della colina sulla chetonuria, Arch. di sc. biol. **24**:396-398, 1938.

4. Paul, W. D.; Daum, K., and Kemp, C. R.: The Action of Choline on the Blood Lipid Fractions in Cirrhosis of the Liver, Diabetes Mellitus and Related Conditions of Disturbed Fat Metabolism, J. Iowa M. Soc. **37**:146-155, 1947.

5. Pelner, L.; Davidson, B.; Waldman, S., and Margolis, R.: The Rôle of Choline Chlorine in the Treatment of Certain Cases of Diabetes Mellitus, New York State J. Med. **48**:523-524, 1948.

Little is known about the choline metabolism in diabetic patients. Lindberg and Möllerström [6] found an increased excretion of choline in the urine of some diabetics. They used the periodate precipitation method of Roman [7] for the analyses. This method is known to possess very little accuracy, giving values that are too high and uncertain even in normal subjects. In the study of the metabolism of choline in diabetic patients, we first investigated the urinary excretion of choline by a more accurate and sensitive method.

EXPERIMENTAL STUDY

Method.—A quantitative estimation of choline in biologic materials can be made only by means of an accurate method which is highly sensitive and specific. The known chemical methods are unsatisfactory in this respect. They have been discussed and criticized in detail by Best and Lucas [2a] and by Borglin.[8] The latter carried out careful investigations with the urine of white rats and of man on a large scale and found that only the biological methods can be used for investigations of this type. Schlegel [9] investigated the choline content of the blood in man and arrived at the same conclusion.

The principle of this method is the acetylation of the choline into the more active acetylcholine and determination of the latter by pharmacologic titration. In the course of this work we selected the biologic method using surviving rabbits intestine for estimation of the acetylcholine. The experiments were carried out mainly in accordance with the description given by Borglin,[8] with slight modifications as described below.

Preparation of Urine: The preparation of the urine samples and the acetylation were carried out exactly according to the technic mentioned. Twenty-four hour samples were collected under toluene from both diabetic and normal persons, the p_H made acid to litmus and 10 cc. samples taken for analysis. The urine was treated with alcohol, centrifuged and the water-alcohol solution evaporated under reduced pressure at 80 to 90 C. to about 0.5 cc. To the residue, 15 cc. of acetic anhydride was added and refluxed on a water bath for twelve minutes (Abdon and Ljungdahl-Östberg [10]). The excess of acetic anhydride was

6. Lindberg, O., and Möllerström, J.: Ueber Cholinausscheidung bei Diabetes mellitus, Naturwissenchaften **31**:65-66, 1943.

7. Roman, W.: Eine chemische Methode zur quantitativen Bestimmung des Cholins und einige physikalisch-chemische Daten des Cholins und seiner Salze, Biochem. Ztschr. **219**:218-231, 1930.

8. Borglin, N. E.: On the Excretion of Choline in Urine, Acta pharmacol. et toxicol. (supp. 1) **3**:1-123, 1947.

9. Schlegel, J. U.: Variationer i serumcholinindholdet hos mennesker, Copenhagen, Ejnar Munksgaards Forlag, 1948.

10. Abdon, N. O., and Ljungdahl-Östberg, K.: A Method for Quantitative Determination of Acetylcholine Precursor and Free Acetylcholine in Tissues, Acta physiol. Scandinav. **8**:103-121, 1944.

distilled off at reduced pressure to about 1 cc. The remaining solution was diluted with several cubic centimeters of distilled water, and the acetic anhydride was removed by means of repeated washing with ether. Finally distilled water was added to the samples until the volume amounted to 15 cc., and they were kept in a refrigerator at —20 C. until the biologic estimation was made.

Preparation of Food Samples: Extraction and acetylation of total choline in food was carried out according to the description given by Fletcher, Best and Solandt.[11] A daily diet for one person was collected, minced and mixed very carefully, the whole amount weighed and 50 Gm. taken for analysis. The sample was refluxed with 500 cc. of 18 per cent hydrochloric acid for one hour. After cooling, the mixture was made up to 1,000 cc. and filtered and 10 cc. treated in the same way as the urine.

Estimation of Choline: The biologic estimation was carried out with rabbit intestine. The animals were killed after being kept for twenty-four hours without food; the duodenum and the upper part of the jejunum were taken out immediately after killing, washed and kept in a refrigerator for twenty-four hours in a physiologic solution of the following composition:

	Gm. or Cc.
Sodium chloride	8.0
Potassium chloride	0.2
Calcium chloride (anhydrous)	0.2
Magnesium chloride (anhydrous)	0.1
Twice distilled water to make	1,000.0

A piece of intestine 10 to 15 mm. long was placed in a 50 cc. Magnus vessel which was mounted in a water bath at temperature of 38 C. The Magnus vessel contained the same physiologic solution with 1 Gm. of dextrose and 1 Gm. of sodium bicarbonate added to each liter. A mixture of 93.5 per cent oxygen and 6.5 per cent carbon dioxide was bubbled through the solution. The contractions of the intestine were registered on a suitable kymograph.

The titration of acetylcholine in the sample was carried out in the following way. The addition of a given amount of the test solution caused a contraction, the height of which was just between the heights of contractions caused by two different known amounts of acetylcholine. The standard solution of acetylcholine used was freshly prepared and contained 1 microgram to each cubic centimeter. Attention was paid to the fact that increasing amounts of acetylcholine produce different contractions, the heights of which give an asymptotic curve. The amounts of test solution and acetylcholine standard solution were therefore selected so that the height of the contractions came within the rising part of this asymptotic action curve. In this way it was easy to obtain the actual rates by simple interpolation. Each amount of known and unknown acetylcholine solution was added at least twice and mean values taken. After each application of standard and test solutions, the intestine in the Magnus vessel was washed twice with the physiologic solution at 38 C.

Accuracy of Estimate: The accuracy of the method was controlled in different ways. In some experiments two parallel samples, each of 10 cc., were taken from the same urine, acetylated and examined separately with different intestines. The results are given in table 1. It will be seen that the highest difference between two parallel estimations

11. Fletcher, J. P.; Best, C. H., and Solandt, O. M.: The Distribution of Choline, Biochem. J. **29**:2278-2284, 1935.

is about 15 per cent. The other question as to the accuracy of the method is whether the choline in the urine samples is completely converted into acetylcholine. This problem was investigated in the following way. A 10 cc. sample of urine was acetylated and the acetylcholine estimated. Then known amounts of choline hydrochloride were added to the same urine and the estimation repeated. The results, given in table 2, show the acetylation to be complete.

Results.—The subjects used in these experiments were given the same hospital diet. This was plentiful (over 3,000 calories daily), and in most cases it was not completely consumed. The total choline content of the daily diet was estimated for two days. The results are given in table 3. A corresponding value could be obtained also by simple com-

TABLE 1.—*Values Obtained in Parallel Estimations of Choline Content in 10 Cc. Samples of Urine.*

Experiment	Choline Content, Micrograms		Difference	
	No. 1	No. 2	μg	Percentage
1	11.4	11.2	0.3	2.7
2	47.2	43.0	4.2	9.8
3	20.0	17.3	2.7	15.5

TABLE 2.—*Determination of Choline Content When a Known Amount of Choline is Added to a 10 Cc. Sample of Urine*

Choline Chloride, Micrograms		Difference Between Calculated and Found	
Added	Found	μg	Percentage
0.0	42.1	...	...
10.0	57.5	5.4	9.4
30.0	78.0	5.9	12.2

putation on the basis of the table given by Borglin,[8] presenting the choline content of the most usual Swedish foods. The choline content of the hospital diet according to this table was calculated for six consecutive days and values from 280 to 780 mg. a day (average 520 mg. a day) were obtained.

Borglin found that the ordinary Swedish hospital diet contains between 300 and 500 mg. of choline daily, on occasional days up to 800 mg. Our own results tally with these figures. Furthermore, Borglin found in investigations on many healthy subjects in Sweden that the daily choline excretion in the urine corresponds to about 0.5 to 1 per cent of the total choline consumed with the food. Regarding these results of Borglin's and our own results given in table 3, it can be assumed that for the patients examined by us normal rates of choline excretion are 5 mg. or less, whereas values over 5.0 mg. indicate

increased choline excretion. Table 4 shows the results of estimations of choline in the daily urine in some diabetic patients and in healthy persons on the same diet. It will be seen that in some cases the amount of choline in the daily urine is much higher than the 5.0 mg. mentioned; in other cases it is within normal limits. The healthy subjects excreted less than 5.0 mg. of choline daily. When the ratio of the excreted choline to the choline consumed with the food is computed as a percentage (on the basis that about 500 mg. of choline is consumed with the food

TABLE 3.—*Choline Content of Daily Hospital Diet*

Days	Coline Content (Bound + Free), Mg.	Mean Value, Mg.
10/29/48	605.0	632.5
	660.0	.....
		548.3
10/30/48	488.0	464.0
	440.0	.....

TABLE 4.—*Excretion of Choline in Urine of Diabetic and of Normal Subjects for Three Consecutive Days*

Subject	No. 1	No. 2	No. 3
Diabetic			
H. J.	10.30 (2.1)*	.....	.....
D. C. O.	14.45 (2.9)	.....	.....
L. K. A.	18.80 (3.8)	.....	.....
J. A.	2.12 (0.4)	.....	.....
G. S. R.	.....	3.90 (0.8)	3.10 (0.6)
S. D. J.	.....	3.10 (0.6)	4.15 (0.8)
C. G.	.....	4.55 (0.9)	2.82 (0.6)
K. O.	0.61 (0.1)	.....	.....
G. A.	.....	2.75 (0.6)	2.80 (0.6)
H. S.	.....	6.30 (1.3)	1.40 (0.3)
D. G.	.....	1.83 (0.4)	.....
B. G.	.....	.....	5.20 (1.1)
Normal			
O. S.	.....	2.91 (0.6)	3.80 (0.8)
T. C.	.....	.....	2.22 (0.4)

* Figures in parentheses represent the ratio between consumed and excreted choline expressed as a percentage on the assumption that 500 mg. of choline is ingested with the food daily.

daily), the values for diabetic subjects are 0.1 to 3.8 per cent and for healthy subjects 0.4 to 0.8 per cent. As previously mentioned, the physiologic values range up to 1.0 per cent. It will be seen also from table 4 that the amount of choline in the daily urine is not stable. Furthermore, it varies so much that it is difficult to obtain a true picture of the choline excretion when only the values for one or two days are considered. Therefore, it was necessary to follow the daily urinary excretion in diabetic and in normal subjects for several days to obtain more figures for statistical evaluation. Table 5 presents the values obtained in experiments of this type. The figures shown in table 5 were

evaluated statistically and the significant differences between the values for each subject are given in table 6. As to the tables 5 and 6, the diabetic subjects can be divided into two groups. One group (patients J. A. and B. A.) had choline excretion which corresponds to the normal.

TABLE 5.—*Urinary Excretion of Choline by Diabetic and by Normal Subjects Over a Period of Several Days*

Subject	Sex	Age, Yr.	Type of Diabetes*	Choline Excretion, Mg. per Day								
Diabetic												
J. A.	F	68	B	2.91	2.12	0.90	1.70	2.03	1.76	2.08	3.63	2.22
B. A.	M	45	A	3.22	1.30	1.08	2.32	2.63	....	....	....	2.12
H. I.	F	69	B	7.40	6.05	5.00	10.30	61.0	8.60	8.26	....	7.40
N. C.	M	42	B	11.88	7.65	10.34	6.76	6.16	10.67	....	....	8.92
L. K. A.	M	69	A	5.30	4.90	4.90	18.80	9.50	10.00	12.00	18.15	10.44
D. K. O.	M	38	A	3.60	6.89	11.34	14.48	20.00	20.93	10.33	11.32	12.35
Normal												
D. J.	M	35	..	0.82	1.25	1.90	1.85	....	....	....	....	1.46
N. N.	M	42	..	1.20	1.65	1.50	2.30	....	....	....	....	1.66
L. G.	M	50	..	1.65	1.70	1.76	2.40	....	....	....	....	1.88

* Type A indicates diabetes with excretion of ketone bodies; type B, diabetes without excretion of ketone bodies.

TABLE 6.—*Mean Values (M), Standard Error of Mean Values (μx) and Significant Differences*

Subject	M	μx *	Significant Differences †								
			J.A.	B.A.	H.I.	N.C.	L.K.A.	D.K.O.	D.J.	N.N.	L.G.
J. A.....	2.22 ± 0.284		....	0.20	5.19	6.15	4.19	4.90	1.99	1.61	1.04
B. A.....	2.12 ± 0.412		0.20	....	5.06	6.03	4.19	4.90	1.36	1.01	0.54
H. I.....	7.40 ± 0.957		5.19	5.06	....	1.07	1.40	2.19	6.00	5.88	5.69
N. C.....	8.92 ± 1.048		6.15	6.03	1.07	....	0.61	1.50	6.92	6.81	6.62
L. K. A.....	10.44 ± 1.940		4.19	4.19	1.40	0.61	....	0.68	4.85	4.48	4.38
D. K. O.....	12.35 ± 2.046		4.90	4.92	2.19	1.50	0.68	....	5.29	5.19	5.10
D. J.....	1.46 ± 0.254		1.99	1.36	6.00	6.92	4.85	5.29	....	1.92	1.39
N. N.....	1.66 ± 0.199		1.61	1.01	5.88	6.81	4.48	5.19	1.92	....	0.85
L. G.....	1.88 ± 0.165		1.04	0.54	5.69	6.62	4.38	5.10	1.39	0.85	....

* $\mu x = \dfrac{\left(\dfrac{\Sigma \Delta x}{\sqrt{n}}\right) 1.25331}{\sqrt{n}}$

† Significant difference $= \dfrac{M_1 - M_2}{\sqrt{\mu x_1^2 + \mu x_2^2}}$

Values above 4.00 are considered statistically significant.

The significant differences between the values for daily choline excretion in these patients and those in normal subjects are 1.99, 1.61, 1.04 and 1.36, 1.01, 0.54 respectively. This means that there is a full agreement between the two groups regarding the choline output. In the other 4 diabetic subjects the rate of choline excretion is higher than normal.

The difference between the two groups is significant statistically in each case, as the values for significant differences are always above 4.00.

COMMENT

The accuracy of the biologic method of choline estimation has been established by several investigations (Best and Lucas,[2a] Borglin [8] and Schlegel [9]), and in our own experiments it was also shown to be reliable, giving true values for the choline content of the urine. As mentioned in the introduction, the aim of this investigation was to obtain an idea as to the choline metabolism in diabetic persons. Very little is known about what happens to choline consumed with the food. It is certain that the choline comprised in the daily diet plays an important part in the fat metabolism; it becomes a part of the lecithin molecule and is partly converted into dimethylaminoethanol, yielding a labile methyl group, and partly oxidized to betaine aldehyde and betaine, but neither its ultimate fate nor the connection between these reactions is completely known. About 0.5 to 1.0 per cent of the choline consumed with the food is excreted unchanged in the urine, whereas 99.0 to 99.5 per cent takes part in the metabolism on other routes. Therefore, if one intends to study the metabolism of choline in diabetic subjects, it is first necessary to investigate the per cent ratio between the choline consumed and that excreted in these subjects.

As a basis for calculation of the excretion of choline in healthy subjects who eat ordinary Swedish food, we took Borglin's results supplemented by some investigations carried out by us. Borglin made many investigations regarding the choline content of foodstuffs and the choline excreted in the urine and found that the usual Swedish diet contains on an average 300 to 500 mg. of choline daily. Normal healthy persons consuming the common Swedish diet eliminate choline in the urine in amounts varying from 2 to 4 mg. daily; in occasional cases only is this average a little higher. These figures represent about 0.5 to 1.0 per cent of the daily choline intake.

The diabetic patients in our hospital had generally had a diet composed of the usual Swedish food, without restrictions as to amount and composition. The amount of choline in a daily portion of this food according to our analyses averaged 564 mg., which represents the highest figure possible, as maximum amounts of food were used for choline estimations. These amounts could usually not be consumed by the patients. By way of control, healthy subjects without metabolic disorders were selected, some of whom were given the same diet, while others ate ordinary Swedish food outside the hospital. All the normal subjects showed an excretion lower than 1 per cent of the daily choline intake. On the average, the values were not higher than 4 mg., and all were lower than 5 mg.

It seems also that under physiologic conditions, the choline output shows only a small variation up to 5 mg. daily. Values averaging over 5 mg. can be taken to indicate an abnormal choline metabolism.

In some diabetic patients [12] we found the choline excretion to be increased for several days, and in this case the means were higher than 5 mg. The difference between the figures obtained for these patients and those obtained for normal subjects was also statistically significant. This means that in such cases one is obliged to assume a pathologic choline metabolism. On the other hand, we found a normal choline output in some diabetic patients, and the figures also agree statistically with those for normal subjects. Our experiments were too few to permit a statement about the percentage of diabetic persons with an increased choline output, nor can we give an opinion about the relation between the level of choline excretion and clinical symptoms of diabetes mellitus. It seems, however, that in the cases investigated no relations obtained between the choline output and the excretion of ketone bodies. This observation needs further confirmation. Also, the question of the influence of insulin on the choline excretion in the urine of diabetic persons needs further investigation.

SUMMARY

The daily choline excretion in the urine was investigated in diabetic and in healthy subjects. The estimation of choline was carried out by acetylating the choline and estimating the acetylcholine with surviving rabbit intestine. In healthy subjects values up to 5 mg. per day were noted, whereas in some persons with diabetes mellitus the choline output was found to have increased and showed a statistically significant difference from the values for normal subjects. No correlation was found to obtain between the level of choline excretion and diabetic symptoms. The importance of an increase in choline excretion as a symptom of disorders in the choline metabolism is discussed.

12. The sodium sulfosalicylate test for albumin in the urine used in this investigation gave negative results in all the diabetic patients.

MULTIPLE HEMORRHAGIC SARCOMA AND DIABETES MELLITUS

Review of a Series, with Report of Two Cases

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MULTIPLE idiopathic hemorrhagic sarcoma is a chronic disease with characteristic cutaneous lesions and, occasionally, widespread internal involvement. It was first described by Kaposi in 1872, and, although the disease is relatively rare, the literature on the subject has been copious. Kren [1] wrote a 113 page monograph with 10 pages of references, and twenty-four synonyms have been listed for the disease. In 1932, Dörfell [2] searched the literature and found reports of 356 bona fide cases, of which only 21 had occurred in females. Choisser and Ramsey,[3] in 1939, stated that 600 cases had been reported since 1872. Persons of Jewish extraction are particularly though not exclusively affected, and most patients come from Russia, Poland, or Italy and are of the laboring class. Lowenthal,[4] in 1938, recorded a case in a full-blooded Negro and stated that only 3 similar cases had been reported previously; Persky and Lisa [5] reported another in 1944.

The disease generally appears after the age of 40, and the highest incidence is in the sixth and seventh decades of life, but it occurs in younger age groups. Denzer and Leopold [6] reported a fatal case in a

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1. Kren, O., in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1933, vol. 12, pt. 3, pp. 891-1004.

2. Dörfell, J.: Histogenesis of Multiple Idiopathic Hemorrhagic Sarcoma of Kaposi, Arch. Dermat. & Syph. **26**:608-634 (Oct.) 1932.

3. Choisser, R. M., and Ramsey, E. M.: Angioreticuloendothelioma (Kaposi's Disease of the Heart), Am. J. Path. **15**:155-178 (March) 1939.

4. Lowenthal, L. J. A.: Multiple Idiopathic Hemorrhagic Sarcoma of Kaposi, Arch. Dermat. & Syph. **37**:972-974 (June) 1938.

5. Persky, B. P., and Lisa, J. R.: Multiple Idiopathic Hemorrhagic Sarcoma of Kaposi in a Full-Blooded Negro, Arch. Dermat. & Syph. **49**:270-272 (April) 1944.

6. Denzer, B. S., and Leopold, H. C.: Idiopathic Hemorrhagic Sarcoma (Kaposi), Am. J. Dis. Child. **52**:1139-1147 (Nov.) 1936.

child of 4½. MacKee and Cipollaro [7] stated that the duration of the disease ranges from one to twenty-five years but that the average patient survives only five to ten years, and that death is often attributable to hemorrhage and emaciation from visceral involvement.

The initial lesions commonly appear on the extremities (especially the legs) as reddish or purplish nodules of firm consistency which may coalesce into infiltrated plaques. Later lesions may appear anywhere on the skin and sometimes on mucous membranes. Pautrier and Diss [8] described a case in which the lesions began as small, colorless, painful hypodermal nodules which were detected only by palpation and later assumed the characteristic violaceous hue. However, the early cutaneous lesions are almost always visible and are not ordinarily painful. In the case reported by Jessup,[9] the only detected lesions were on the scalp and forehead, and sections showed cells invading the lumen of a large vein.

Autopsies have frequently shown that almost any organ may be invaded. In a number of instances, there has been visceral involvement without any demonstrable changes in the skin. Choisser and Ramsey [3] described 2 curious cases without cutaneous lesions in which tumors located within the right auricle caused a ball valve type of obstruction at the tricuspid orifice which was rapidly fatal. Aegerter and Peale [10] recorded a case in which death resulted from a 1,000 cc. tamponade due to hemorrhage and stated that when the disease was primarily of the viscera it was usually not present in the skin. Nesbitt and others,[11] in 1945, observed disseminated lesions in a fatal case without cutaneous involvement and noted that in no previously reported case had a patient shown lesions of the brain and the thyroid gland. Dörfell [2] mentioned that the pancreas is not infrequently involved.

Kaposi's sarcoma and the lymphomas occasionally appear together, as in the case of Sachs and Gray,[12] in which lesions of Kaposi's sarcoma were noted in the upper cutis and an infiltrate of lymphatic leukemia was evident in the lower cutis. Death was attributed to the leukemia. In

7. MacKee, G. M., and Cipollaro, A. C.: Idiopathic Multiple Hemorrhagic Sarcoma (Kaposi), Am. J. Cancer **26**:1-28 (Jan.) 1936.

8. Pautrier, L. M., and Diss, A.: Kaposi's Idiopathic Sarcoma Is Not a Genuine Sarcoma but a Neurovascular Dysgenesis, Brit. J. Dermat. **41**:93-105 (March) 1929.

9. Jessup, D. S. D.: Kaposi's Sarcoma, Am. J. Cancer **31**:556-562 (Dec.) 1937.

10. Aegerter, E. E., and Peale, A. R.: Kaposi's Sarcoma, Arch. Path. **34**:413-422 (Aug.) 1942.

11. Nesbitt, S.; Mark, P. F., and Zimmerman, H. M.: Disseminated Visceral Idiopathic Hemorrhagic Sarcoma (Kaposi's Disease): Report of Case with Necropsy Findings, Ann. Int. Med. **22**:601-605 (April) 1945.

12. Sachs, W., and Gray, M.: Kaposi's Sarcoma and Lymphatic Leukemia, Arch. Dermat. & Syph. **51**:325-329 (May) 1945.

another case, reported by Lane and Greenwood,[13] the patient had cutaneous lesions of both Kaposi's sarcoma and mycosis fungoides and a blood picture of lymphatic leukemia.

The histopathology of the disease varies in the different stages, so a microscopic diagnosis is at times difficult. MacKee and Cipollaro[7] pointed out that inflammatory, granulomatous and neoplastic stages evolve in that order. The early lesions are largely angiomatous with new and dilated blood vessels and lymph vessels associated with edema, hemorrhage and cellular infiltration. In the later stages, the vascular sinuses become indistinct and fusiform cells proliferate; affected areas may easily be confused with the lesions of fibrosarcoma. The process in the viscera is often less angiomatous and is frequently of a pure spindle cell type.

The etiology still remains obscure. Many authors have stated the belief that the lesion is a true neoplasm, whereas others regard it as an infectious granuloma, and some consider it to be of the nature of a hamartoma derived from germ plasm. Dörfell,[2] after studying the histogenesis of the disease, concluded that it was a disorder of the reticuloendothelial system including a disturbance of its monocytic function which might at times terminate in true malignancy. Pautrier and Diss[8] described structures resembling the myoneuroarterial glomus and bodies similar to Meissner corpuscles and called the disease a dysgenesis of the vessels and their neuromuscular annexes on the one side and their schwannian elements on the other. It is debatable whether visceral lesions arise in situ or represent true metastases. Of those who have done experimental work, only Justus[14] reported success in animal inoculations. He claimed to have inoculated a mouse with a rapidly growing lesion and to have carried a lesion through five generations of rabbits. Becker and Thatcher[15] obtained an abundant growth of spindle cells from the culture of a benign lesion; subsequent implantation under the patient's skin gave rise to a plaque of Kaposi's sarcoma, but implantation into rabbits produced negative results. Dillard and Weidman[16] found myceliums and chlamydospores in the mesenteric and omental lymph nodes in a case in which the patient had disseminated lesions but did not claim the fungus to be the cause of the disease.

13. Lane, C. G., and Greenwood, A. M.: Lymphoblastoma (Mycosis Fungoides) and Hemorrhagic Sarcoma of Kaposi in the Same Person, Arch. Dermat. & Syph. **27**:643-654 (April) 1933.

14. Justus, J.: Über Übertragung von Sarcoma idiopathicum hæmorrhagicum Kaposi auf Tiere, Arch. f. Dermat. u. Syph. **99**:446, 1910; Sarcoma idiopathicum Kaposi, ibid. **151**:436, 1926.

15. Becker, S. W., and Thatcher, H. W.: Multiple Idiopathic Hemorrhagic Sarcoma of Kaposi, J. Invest. Dermat. **1**:379-398 (Oct.) 1938.

16. Dillard, G. J., and Weidman, F. D.: Multiple Hemorrhagic Sarcoma of Kaposi, Arch. Dermat. & Syph. **11**:203-231 (Feb.) 1925.

REVIEW OF STUDIES

The records of the Presbyterian Hospital since 1928 were searched, and reports of 13 cases of Kaposi's sarcoma were found in which the diagnosis was certain. All the patients were males, and only 2 were born in the United States. Of these 2, one was born of Russian Jewish parents. Of the remaining 11, 5 were Russian Jews, 2 were German or Austrian Jews, 3 were Italians and 1 was a Hungarian. The age of the youngest at onset was 19, and that of the oldest 74.

The table shows the decade of life in which cutaneous lesions first appeared in this group of cases. Six of the 13 patients are now dead. In 3 cases, death was attributable to Kaposi's sarcoma. The remainder of the patients died of carcinoma of the sigmoid colon, carcinoma of the bronchus or acute meningitis; so Kaposi's sarcoma was not a direct contributing cause. The duration of the disease in the 6 fatal cases ranged from two to twelve years with an average of five and a half years. For the patients still living at the time of the last observation,

Age of 13 Patients at Onset of Kaposi's Sarcoma

	Age, Years						
	11-20	21-30	31-40	41-50	51-60	61-70	71-80
Number of patients.....	1	0	0	5	4	2	1

the duration ran from two to twenty years; the average was nine and a half years.

In this series of cases, pitting edema of the extremities (particularly of the legs) was a frequent finding, and in 6 cases it occurred early in the disease and either preceded or appeared shortly after the skin lesions. In 3 cases it was a late manifestation. Edema of the leg for a year was the presenting complaint of a patient in whose case considerable study and observation failed to establish a diagnosis until cutaneous lesions made their appearance. A case was also recorded in which edema of the hands and arms preceded any involvement of the skin. In another instance, there had been edema of the right leg for four or five years when a lesion on the plantar surface of the left foot was diagnosed as melanoepithelioma and a radical excision of the femoral and inguinal lymph nodes was performed. Later, a lesion appeared on the skin of the right foot; the histopathologic picture was that of Kaposi's sarcoma.

In a number of cases, evidence of the disease was found beyond the skin prior to death. Several patients showed invasion of the axillary or inguinal lymph nodes, and 1 showed lymphatic involvement of the lungs on roentgenologic examination.

Eosinophilia was not a consistent finding, but a differential count of 4 or 5 per cent eosinophils in a normal total leukocyte count was not

uncommon; occasional readings up to 17 per cent were recorded. Monocytosis, as reported by some authors, was not observed in this series.

In the case of the 1 young patient in this series who subsequently died of Kaposi's sarcoma, cultures on various mediums and inoculations of animals with tissue removed for biopsy failed to yield positive results.

It was noted that 6 (46 per cent) of the patients with Kaposi's sarcoma showed evidence of diabetes mellitus.[17] Three patients had frank diabetes requiring diet and insulin for control. In the mildest case 20 units of insulin daily sufficed, and in the severest case up to 60 units a day were required. Two patients showed only glycosuria (2 plus and 4 plus, respectively), but their cases were not adequately studied from the standpoint of diabetes. However, 1 of these patients gave a history of having had diabetes diagnosed six months previously and most probably had true diabetes. The remaining patient (the one in case 2 in the present report) showed glycosuria on only one occasion, but the reaction to the dextrose tolerance test was definitely diabetic in type. Two of the 6 patients had recognized diabetes prior to the diagnosis of Kaposi's sarcoma. In the remaining cases, the evidence of diabetes appeared after the cutaneous lesions.

The 2 reports illustrate the occurrence of Kaposi's sarcoma in a case of frank diabetes and in 1 of potential diabetes. Autopsy findings are included in case 1.

REPORT OF CASES

CASE 1.—J. O., a Russian Jewish salesman of 49, entered Vanderbilt Clinic in September 1930, with a complaint of swelling of the right foot and leg for two years and nodular cutaneous lesions of four months' duration. He stated that several similar nodules had been "burned off" six months previously. The patient's father had died of carcinoma of the stomach, and 1 sister had mild diabetes.

The patient had been born in Russia but had lived in the United States for the past thirty-five years and, in general, had always enjoyed good health. The veins in both legs had been somewhat prominent since childhood but had caused no symptoms.

Physical Examination.—Physical examination disclosed twelve firm, nontender, purplish nodules, 4 to 10 mm. in diameter, on the right leg between the ankle and midcalf. Some were elevated 5 mm. above the surface of the skin, and some blanched slightly on pressure. The right foot and leg were firm, edematous and cooler to the touch than the left ones. The circumference of the right leg 9 cm. below the tibial tubercle was 41 cm., and that of the left leg was 38 cm. The circumference 8 cm. above the medial malleolus was 30 cm. on the right and 24.5 cm. on the left. There was only slight varicosity of the internal saphenous veins. No lymphadenopathy was noted, and except for moderate obesity and a blood pressure of 150 systolic and 98 diastolic (later 190 stystolic and 90 diastolic) the remainder of the examination gave normal results.

Microscopic Examination.—Tissue was taken from one of the lesions. The report of the histologic examination, read on Nov. 19, 1930 by Dr. A. P. Stout, was as follows:

17. Dr. George C. Andrews made this observation.

"The swelling was due to a complicated growth composed of many capillaries containing blood and lined with swollen endothelial cells which were often seemingly several layers thick. The capillaries were surrounded by rather large spindle-shaped cells, arranged in bundles, which tended to interlace. The nuclei were ovoid and somewhat hyperchromatic, and mitoses averaged one to every two or three high power fields. Many of these cells were surrounded by

Fig. 1.—Cutaneous lesion in case 1 at a relatively early stage, showing angiomatous features. Low power field.

slender collagen fibers which were argyrophil. Other cell groups had no fibers between them. In general, when the cells were surrounded by fibers they were silver negative with Laidlaw's stain, but when they were gathered in groups they were silver positive. In some of the septums of connective tissue which separated the masses of cells and capillaries, there was blood pigment. In other places, some cells of the main tumor groups contained finely divided pigment which was blackened by the Fontana stain and which was probably melanin. About the

periphery of the main tumor mass was an advance guard of capillaries, suggesting that that was the method by which the growth extended" (figs. 1 and 2).

Course.—Roentgen therapy was begun, a dose of 300 r being given to different areas of the skin at varying intervals as needed to reduce the lesions. The factors used were 160 to 180 kilovolts, 4 milliamperes, 50 cm. target-skin distance and a filter of 0.25 mm. of copper and 1 mm. of aluminum. During the ensuing years, a total of 22,200 r was given, divided among six areas on the right leg.

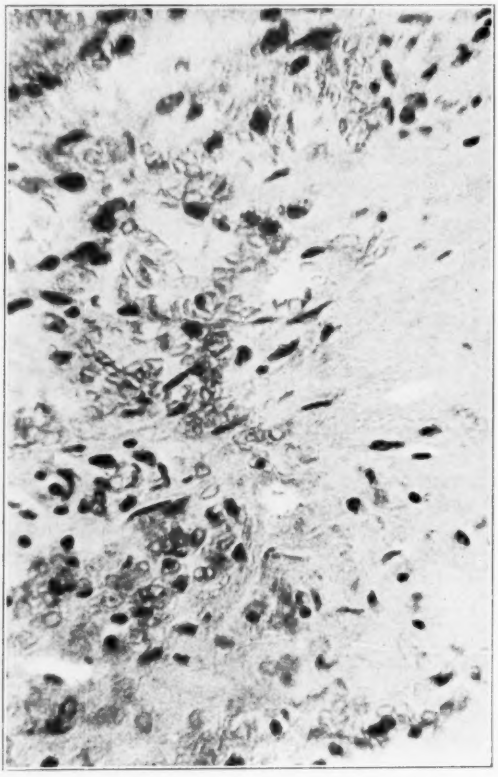

Fig. 2.—Cutaneous lesion in case 1. High power field.

In November 1930, glycosuria was discovered (4 plus); the fasting blood sugar was 244 mg. per hundred cubic centimeters of blood. The patient was given a diet of 185 Gm. of carbohydrate, 70 Gm. of protein and 60 Gm. of fat, and 25 units of protamine zinc insulin was given after breakfast. Over the period of more than ten years that the patient was observed, the diabetes was fairly well controlled with essentially the same diet and insulin dosage, and new cutaneous lesions which appeared from time to time responded well to

roentgen therapy. On occasion the patient was free of cutaneous lesions, but there was a brawny discoloration from treatment, and the edema of the leg persisted.

During that time, roentgenograms of the legs, chest and gastrointestinal tract showed a normal condition. The value for total serum cholesterol was 197 mg. and that for urea nitrogen 7 to 15 mg. per hundred cubic centimeters. The Wassermann

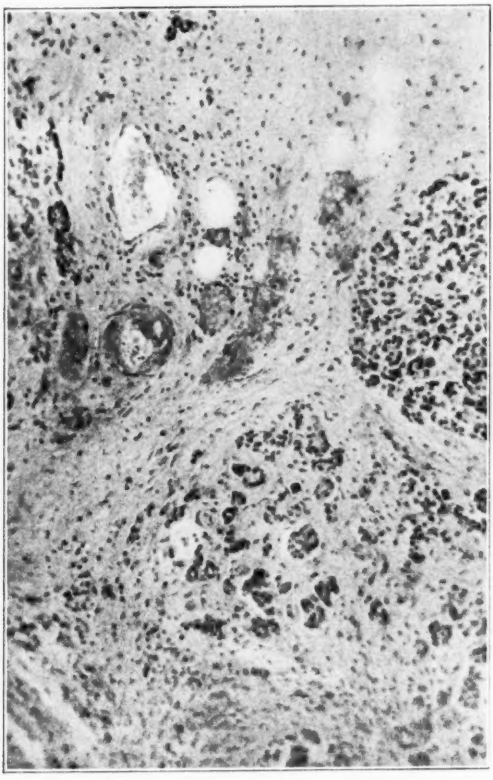

Fig. 3.—The pancreas in case 1. Low power field.

reaction of the blood was negative. Repeated blood counts did not give remarkable results except for occasional eosinophilia, which ranged as high as 7 per cent.

On June 26, 1941, otitis media due to pneumococcus type III developed, and this was followed, on July 21, by mastoiditis, for which mastoidectomy was performed. Meningitis subsequently developed, with pneumococcus type III in the spinal fluid. A subdural exploration revealed no pus. In spite of treatment with immune serum and sulfapyridine, the patient died on July 31.

Necropsy.—Necropsy revealed acute leptomeningitis, generalized arteriosclerosis with sclerosis of the coronary arteries and sclerotic scars in the kidneys, fatty degeneration of the liver and hyalinization of the islets of Langerhans. There were extensive brownish discoloration and brawny edema of the right leg, and on the skin were several hard, bluish, shotty nodules, 2 to 4 mm. in diameter, but no definite internal lesions of Kaposi's sarcoma were found. Sections of the pancreas at one end showed acini together with one or two islets, around which was

Fig. 4.—Cutaneous lesion in case 2 at a late stage, showing mononuclear and spindle-shaped cells. Low power field.

an invasion of fibrous tissue. The acini were separated from one another by invasions of fibroblasts, and numerous capillaries and many young fibroblasts were seen. There was hyalinization of the walls of the arterioles, and a number were partially thrombosed. Some of these findings were compatible with those in cases of long-standing lesions of Kaposi's sarcoma, but in this case, in which arteriosclerosis, hypertension and diabetes were present, they were most probably the result of vascular changes (fig. 3).

CASE 2.—M. E., a Russian Jewish real estate salesman of 50, presented himself at the Vanderbilt Clinic in December 1937, stating that a purplish red area had developed seven years previously on the skin of the left ankle. During the next three years, dime-sized to dollar-sized purple plaques and nodules appeared on both legs, and the toes assumed a frostbitten appearance which persisted. In the three years before admission to the clinic, similar lesions had involved the trunk, arms, and face, and the patient had noticed swelling of the ankles, which was reduced after a night's rest. On occasions, he had felt slight, transient stinging sensations in the lesions but had not thought them painful.

The family history was noncontributory. The patient had been born in Minsk, Russia, and had come to the United States as a child. Except for slight exertional dyspnea during the past few years, general good health had prevailed.

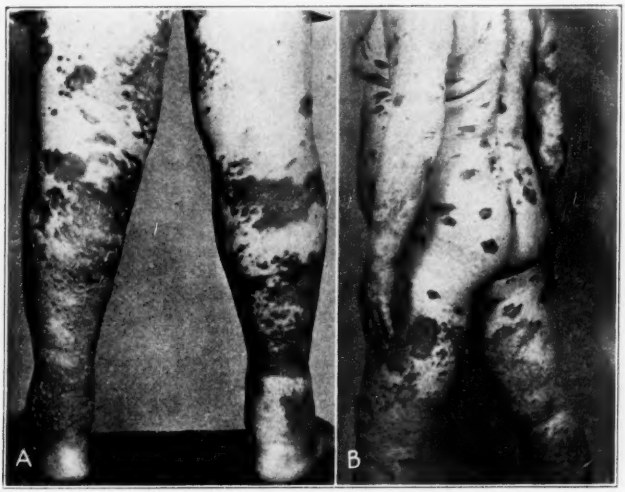

Fig. 5 (case 2).—The patient, *A*, in September 1945; *B*, in January 1947.

Physical Examination.—Examination showed irregular, indurated plaques and nodules of a purplish color scattered over the feet, legs, hands, forearms and chest. The lesions varied in size up to 5 cm. in diameter and were not tender. On the chin was a reddish macule 1 cm. in diameter. Both ears were greatly thickened and of a bluish tint. The ankles and legs showed some pitting edema. Except for moderate obesity, the results of the remainder of the examination were essentially normal.

Microscopic Examination.—On December 24, a biopsy was taken on a lesion on the right leg. Dr. G. F. Machacek's report was as follows:

"These sections showed a moderate hyperkeratosis with no distinct changes in the epidermis. The corium showed pronounced vascular and perivascular changes, and the walls of many vessels were thickened. About them, there was an increase of spindle-shaped cells and also a focal infiltration of mononuclear cells. Here and there, a few red blood cells were scattered through the tissue,

and there were also accumulations of coarse granules of brown pigment which were chiefly intracellular" (fig. 4).

Course.—The patient has been seen frequently at the Vanderbilt Clinic for almost eleven years at the time of writing, and his case has received extensive study. Roentgenograms showed the stomach and the entire skeleton normal, as were results of repeated roentgen examinations of the chest and teeth, and electrocardiograms. The basal metabolic rate was minus 7 per cent, and the Kline reaction was negative. Extensive blood chemistry studies were within normal limits, and bleeding and clotting times and platelet counts were not abnormal. Numerous blood counts did not give remarkable results except of a frequently high eosinophil count, which was once 17 per cent and on two occasions 13 per cent.

Although urinalysis and determinations of fasting blood sugar were normal, the reactions to a glucose tolerance test made in May 1941 were of the diabetic type indicated:

Time After Administration of Glucose, Hours	Blood Sugar, Mg. per 100 Cc.	Urinary Reduction
Fasting	120	—
½	188	++
1	232	++++
2	208	+++
3	133	··

On June 1, the patient was admitted to the Presbyterian Hospital for six weeks for study of the effect of insulin therapy on the Kaposi sarcoma. He was given a diet of 175 Gm. of carbohydrate, 80 Gm. of protein and 60 Gm. of fat, with insulin in gradually increasing quantities up to 50 units daily, which he tolerated well. In spite of this large amount of insulin, most determinations of blood sugar were within normal limits. The patient continued to take insulin at home until October 15, when its use was discontinued as no appreciable improvement in the cutaneous lesions could be noted.

In April 1942, a small, pedunculated tumor on the retropharynx was removed; this showed a microscopic structure of Kaposi's sarcoma. New cutaneous lesions appeared from time to time (fig. 5*A*).

In the fall of 1946 the patient began to notice tenderness of the breasts and hot flushes, and by January 1947 there was definite mammary hypertrophy (fig. 5*B*). A determination of the urinary 17-ketosteroids showed a normal value of 9 mg. in a twenty-four hour specimen. The patient was given 25 mg. of testosterone propionate intramuscularly twice a week and noted improvement of the symptoms. In September 1947, he entered the Presbyterian Hospital because of lower abdominal pain and tenderness, and a barium sulfate enema showed the presence of diverticula. There was a 1 plus degree of glycosuria. The following month the patient suffered a rupture of a diverticulum of the sigmoid colon, and a resultant peritoneal abscess was drained of 2,000 cc. of purulent fluid; he made a satisfactory recovery. In August 1948, the left lacrimal duct was excised because of chronic swelling, and examination showed a structure suggestive, but not diagnostic, of Kaposi's sarcoma.

The judicious use of roentgen therapy benefited the patient more than any other form of treatment. In December 1937, the administration of 150 r twice weekly to various cutaneous lesions as needed was begun, and by July 1938 he was much improved, only pigmentation remaining at the sites of many of the lesions. However, new lesions continued to appear, some of which were described as nodular, pedunculated or lichenoid. Roentgen therapy was promptly instituted. The factors for most treatments were 135 kilovolts, 5 milliamperes, 14 to

25 cm. target-skin distance and a filter of 3 mm. of aluminum. Representative of the average dose was the 2,250 r given from December 1937 to December 1945 and directed to numerous individual lesions on the legs.

Other treatments given the patient at different times consisted of the administration of acetarsone (stovarsol®), vitamin K preparations, gold sodium thiosulfate and solution of potassium arsenite (Fowler's solution). None of these medications appeared to be of appreciable benefit.

The patient had steadily maintained that sunlight caused improvement of the cutaneous lesions. In August 1948, after returning from California, where he took frequent sun baths, his skin showed considerable improvement and he appeared robust and optimistic. However, it was noted that improvement had begun about the time the feminizing changes made their appearance, and that no new cutaneous lesions had developed since. In addition to the hot flushes and the enlargement of the breasts, he had loss of libido and his usual heavy growth of body hair had become relatively sparse. He had neglected to take testosterone propionate except at irregular intervals. In October, no new lesions were present and, at the sites of a number of old lesions, the skin appeared almost normal. The ears had lost almost all induration. A few old nodular lesions on the legs appeared to be undergoing involution, and the brawny induration was somewhat decreased. Moderate edema still existed, however, particularly around the ankles.

Additional studies showed a basal metabolic rate of minus 11 per cent and 203 mg. blood cholesterol per hundred cubic centimeters. A twenty-four hour urine specimen showed 21 micrograms of estrogen and 4 mg. of 17-ketosteroids per hundred cubic centimeters. The value for serum chloride was normal, and a roentgenogram of the skull revealed a normal sella turcica. A glucose tolerance test showed decreased tolerance, although the reaction was not so pronounced as previously.

COMMENT

The high incidence of diabetes mellitus in this group of 13 cases of Kaposi's sarcoma appears to be more than a coincidence, and it is believed that patients with this disease should be studied with diabetes in mind. The reason for the coexistence of the two diseases is not apparent, and the cutaneous lesions of Kaposi's sarcoma do not appear to be affected by the administration of insulin. The possibility of an endocrine imbalance in cases of this condition is illustrated in case 2. Although a diagnosis of diabetes was not made in this case, the results of the glucose tolerance test and the high dosage of insulin which the patient was able to utilize suggest the presence of an abnormal anti-insulin factor. The fact that definite clinical improvement in this case began with the onset of spontaneous feminizing changes and that the disease is rare in women gives support to the rationale of treating these patients with estrogenic hormones. Although several patients in the group were treated for long periods with diethylstilbestrol without showing pronounced benefit, further study of the disease from an endocrinologic standpoint seems worth while. As far as could be determined, in the recent literature no mention has been made of diabetes mellitus associated with Kaposi's sarcoma with the exception

of the case reported by Pohle and Clark [18] under the title of "Kaposi's Sarcoma or Lymphogranulomatosis Cutis." The clinical and histopathologic observations in their case would make the condition described appear to be Hodgkin's disease rather than Kaposi's sarcoma.

In the presence of unexplained edema of the extremities, and especially of the legs, Kaposi's sarcoma should be considered as a possibility. Almost half the patients in this series showed edema of the legs as an early symptom, and in a number of cases it appeared before any cutaneous lesions and caused the clinicians to entertain such diagnoses as filariasis or arteriovenous fistula. Apparently the cause of the edema has not been extensively studied, but it would seem to arise from lymphatic obstruction, and in the later stages vascular stasis is superimposed. The disease is not always easily diagnosed, even in the presence of cutaneous lesions, as evidenced by 1 case in which it was confused with melanoepithelioma. The wide variation in the histologic picture of lesions in different stages of development is illustrated in the 2 cases described. Roentgen therapy, although not curative, is by far the most effective form of treatment to date.

SUMMARY

Thirteen cases of Kaposi's sarcoma are reviewed. Six patients, or 43 per cent, either had frank diabetes or showed some evidence of that disease.

Two typical cases are described in some detail, 1 with autopsy findings.

One patient showed definite sustained clinical improvement following the onset of spontaneous feminizing changes.

18. Pohle, E. A., and Clark, E. A.: Kaposi's Sarcoma or Lymphogranulomatosis Cutis (Report of a Case Treated with Roentgen Rays), Urol. & Cutan. Rev. **51**:382-385 (July) 1947.

CLINICAL MANIFESTATIONS OF CARRIÓN'S DISEASE

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CARRIÓN'S disease is caused by Bartonella bacilliformis, a polymorphous organism classified as a bacterium in 1927 by Noguchi,[1] transmitted by sandflies of the genus Phlebotomus. The disease is limited geographically to certain areas of the Andean regions in Peru, Colombia and Ecuador.

The disease is extremely polymorphic in symptoms. The confusion existing in the literature arose in part from reports prior to the discovery of B. bacilliformis, when intercurrent infections were not recognized and many symptoms were erroneously assigned to Carrión's disease. The present report is based on a study made on several hundred cases in Lima, Peru, during the period 1938 to 1943.

HISTORY AND NOMENCLATURE

Archeologic findings indicate that the disease was known in Peru in the pre-Incaic era. Surprisingly accurate representations of the cutaneous nodules, or verrugas, are found in the Peruvian ceramic pots called *huacos*, especially in the Chimu civilization.[2] The first medical publication on the disease is credited to Gago de Vadilla in 1630.[3]

The first Spanish colonizers to arrive in Coaque, Ecuador, described a disease called *bubas* or *berrugas* which greatly resembles Carrión's disease.[4] Apparently in the Keshua language used by the Indians, the

From the Frank Billings Medical Clinic, Department of Medicine, University of Chicago.

The clinical observations were carried out at the Hospitals "Dos de Mayo," Arzobispo Loaiza, San Bartolome, Maternidad, and "del Niño" in Lima, Peru.

1. Noguchi, H.: The Etiology of Verruga Peruana, J. Exper. Med. **45**:175, 1927.

2. La céramique péruvienne de la société d'études Americans, congress international des Americanistes, Compt. rend. d trois. Sess. Brux. **1**:470, 1879. Lastres, J. B.: La semiologia en el Peru, Rev. méd. peruana **7**:421, 1935.

3. Valdizan, H.: Apuntes para la historia de la verruga peruana, An. Fac. med., Lima, numero extraordinario, 1925, p. 34; Apuntes para una bibliografia peruana de la enfermedad de Carrión, ibid., 1925, p. 45.

4. Rebagliati, R.: Verruga peruana (enfermedad de Carrión), Lima, Imprenta Torres Aguirre, 1940.

presence of verrugas was known as *Kceppo* [5] and *Sirki*.[6] Because of the characteristic presence of nodules in the skin, Bueno [7] in 1764 referred to it as the disease of *berrugas*. Tschudi,[8] in 1845 called the lesions "blood verrugas" because of the marked vascularity of the nodules; they are also called "warts of the Andes" [9] because of the prevalence of the disease in these mountains. As the disease was first thought to exist only in Peru, it had the name verruga peruana (verruca peruviana).

All data referred to the cutaneous manifestations, the verrugas, until 1870, when during the building of the Central Railway from Lima to Oroya, in many of the workers a severe anemia and fever developed, the nature of which was unknown. This disease, which produced a mortality of nearly 7,000, was given the name of Oroya fever. This is a misnomer, since the disease does not exist in the Peruvian city of Oroya. Espinal, a Peruvian clinician, in his unpublished clinical lectures, made an accurate observation of the course of the anemic patients and noted that in some verrugas later developed in the skin. He suggested that the two features were probably manifestations of the same disease. In 1885, Daniel A. Carrión, a medical student at the University of San Marcos in Lima, Peru, sacrificed his life to show the relation of Oroya fever to verruga peruviana. He was inoculated by a classmate with the blood from one of the verrugas of a patient. Twenty-one days later a very marked anemia, fever and other manifestations of Oroya fever convinced the attending physicians of Lima that the two conditions were merely different phases of the same disease.[10] Numerous clinical studies followed, and in 1898 Odriozola published an excellent and complete monograph on the disease.[11]

In 1909, Alberto Barton, another Peruvian physician, described with great accuracy the pathogenic organisms in the circulating erythro-

5. Vargas-Fano, J. A.: La verruga peruana a travez de la historia, Thesis, Lima, 1938.

6. Matto, D.: Discurso, Crón. méd., Lima **3**:377, 1886.

7. Bueno, C., Cited by Rebagliati.[4]

8. (*a*) von Tschudi, J. J.: Die Verrugas, Arch. f. physiol. Heilk. **4**:378, 1845. (*b*) Ueber die geographische Verbreitung der Krankheiten in Peru: Mitgetheilt von Dr. Endlicker, Oesterr. med. Wchnschr., 1846, pp. 373, 407, 437, 467, 507, 537, 595, 627, 656, 661, 694 and 725. (*c*) Tupper.[21]

9. Bordier, A.: La geographie médicale, Paris, C. Reinwald, 1884. Salazar, T.: Historia de las verrugas, Thesis, Lima, 1858.

10. (*a*) Medina, C.; Mestanza, E.; Arce, J.; Alcedan, M., and Miranda, R.: La verruga peruana y Daniel A. Carrión, Lima, 1886; An. Fac. med., numero extraordinario, 1925. (*b*) Alcedan, M.: Enfermedad de Carrión, Crón. méd., Lima **3**:381, 1886.

11. Odriozola, E.: La maladie de Carrion, ou la verruga péruvienne, Paris, G. Carré & C. Naud, 1898.

cytes.[12] Skepticism in accepting this organism as the causative factor in the disease was due primarily to the fact that other bacteria, reported earlier by the same author as the pathogenic organisms,[13] were later demonstrated to be due to an intercurrent paratyphoid infection.[14]

Jadassohn and Seiffert [15] in 1910 proved the infectious nature of the verrugas by transmitting the disease in monkeys; their studies were later confirmed.[16] A dual concept of the disease was described by Strong [17] and associates in 1913. These authors recognized B. bacilliformis as the pathogenic agent of Oroya fever but not of the verrugas, which they supposed represented a different disease altogether. In 1925 Noguchi and Battistini [18] were able to culture B. bacilliformis. A year later the same authors [19] were able to culture the bartonella organisms from the verrugas of monkeys, thus proving Espinal's unitary concept of the disease.

The term "malignant" has been applied with different meanings in Carrión's disease: to the fatal cases with verrugas,[7] to the fatal anemic forms [11] and also to particular cases in all different stages of the disease.[20] The terms "benign" and "malignant" still used in Carrión's disease should be discarded, since they have been used for different purposes by various authors and are meaningless.

CLINICAL COURSE

In Carrión's disease there are several stages—incubative, invasive, preeruptive and eruptive.

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12. Barton, A. L.: Descripción de elementos endo-globulares hallados en los enfermos de fiebre verrucosa, Crón. méd., Lima **26**:7, 1909.

13. Barton, A. L.: El germen patógeno de la enfermedad de Carrión, Crón. méd., Lima **18**:193 and 310, 1901; **19**:348, 1902.

14. Tamayo, M. O.: Apuntes sobre la bacteriología de la enfermedad de Carrión, Crón. méd. Lima **22**:335, 1905.

15. Jadassohn, and Seiffert, G.: Ein Fall von Verruga peruviana: Gelungene Uebertragung auf Affen, Ztschr. f. Hyg. u. Infektionskrankh. **66**:247, 1910.

16. (*a*) Mayer, M.; Rocha-Lima, H., and Werner, H.: Investigaciones sobre la verruga peruana Crón. méd., Lima **30**:193, 1913. (*b*) da Rocha, H.: Zur Histologie der Verruga peruviana, Verhandl. d. deutsch. path. Gesellsch. **16**:409, 1913.

17. Strong, R. P.: Report of the First Expedition to South America, Cambridge, Mass., Harvard University Press, 1913.

18. Noguchi, H., and Battistini, T.: Etiology of Oroya Fever: II. Cultivation of Bartonella Bacilliformis, J. Exper. Med. **43**:851, 1926.

19. Noguchi, H.: Etiology of Oroya Fever: II. The Viability of Bartonella Bacilliformis in Cultures and in the Preserved Blood and an Excised Nodule of Macacus Rhesus, J. Exper. Med. **44**:533, 1926; Etiology of Oroya Fever: III. The Behavior of Bartonella Bacilliformis in Macacus Rhesus, ibid. **44**:697, 1926; IV. The Effect of Innoculation of Anthropoid Apes with Bartonella Bacilliformis, ibid. **44**:715, 1926.

20. Arce, J.: Apuntes sobre la enfermedad de Carrión, Crón méd., Lima **30**:325, 1913.

1. *Incubation Period.*—The length of the incubation period has been subject to much controversy. Tupper [21] in 1877 reported a fluctuation of few days to several months, whereas Carrión [10b] considered that it lasted from eight to forty days. The first experimental human observation, made by Carrión on himself in 1885, indicated a twenty-one day incubation before the appearance of the acute febrile anemia which led to his death.[10b] Prior to this, the beginning of the eruption of the verrugas, or what is today called the preeruptive stage, was mistaken as the incubation period. Antunez [22] reported seven to twenty-one days as the incubation period; Arce,[23] from twelve to forty days, and Odriozola,[11] fifteen to forty days. The last-named author denied that the incubation could be of many months' duration, an opinion shared by other authors.[24] An accidental inoculation was followed by onset of the disease twenty days later,[4] Kuczinski [25] made a second experimental self inoculation, the initial symptoms appearing seventeen days later. Mackehenie [26] showed that marked variability can occur, as he observed cases without any symptoms suggesting the disease but with blood cultures positive for B. bacilliformis. In a previous study of 13 cases [27] when blood specimens were cultured for B. bacilliformis on Geiman medium,[28] I found that the period of incubation varied from nineteen to one hundred days.

The difficulties in determining the duration of the incubation period were based primarily on the very limited number of observations and of the lack of reliability of the patients' histories. The disease frequently has a variable symptomatology and occasionally is without symptoms during its entire course, making it very difficult or impossible to diagnose without blood cultures. Battistini,[29] Weinman,[30] Weinman and Pinker-

21. Tupper, F. P.: Ueber die Verruca peruviana, Berlin, g. Schode, 1877; Rev. méd. de Chile, pp. 271, 293, 330 and 353 1878-1879.

22. Antunez, D.: Enfermedad de Carrión, Crón. méd., Lima **7**:290, 1890.

23. Arce, J.: Verrue péruvienne ou maladie de Carrion, Rev. Sud.-am. de méd. et de chir. **2**:1017, 1931.

24. Castillo, J. C.: Verruga peruana, Crón. méd., Lima **11**:259, 275, 289 and 305, 1894.

25. Kuczinski, G. M.: La inmunidad fisiológica, Reforma med. **23**:277, 313, 609 and 648, 1937.

26. Mackehenie, D.: La verruga peruana y la familia tifo-exantematics, An. Fac. med., Lima **18**:245, 1935.

27. Ricketts, W. E.: Carrión's Disease: A study of the Incubation Period in Thirteen Cases, Am. J. Trop. Med. **27**:657, 1947.

28. Geiman, Q.: New Media for the Growth of Bartonella Bacilliformis, Proc. Soc. Exper. Biol. & Med. **47**:329, 1941.

29. Battistini, T., Estudio sobre la verruga peruana, Bol. dir. salub. pub. Lima, 1927, p. 191.

30. Weinman, D.: Reservoirs of Bartonella Bacilliformis and Asymptomatic Human Bartonellosis, Proc. Pacific Sc. Cong. **5**:781, 1939.

ton [31] and Hurtado [32] have demonstrated that persons without symptoms may have the disease. Atypical symptoms during the invasive stage include headache, pain in the bones and joints and moderate fever lasting for a few days. In many cases, such vague and indefinite symptoms are incorrectly interpreted as "flu," "gastrointestinal upsets," etc.[33]

2. *Invasive Stage.*—The features of the invasion vary with respect to symptoms, duration and prognosis; however, clinically, the predominant symptoms are fever and anemia, although they may sometimes be absent. The onset of the disease, as described in a previous paper,[33] may develop insidiously with anorexia, slight fever, headache, malaise, frequently lasting from two days to one week or longer; or it may start suddenly with chills, high fever, copious sweating, headaches and occasionally delirium. The chills never exhibit the definite periodicity typical of malaria. It is important to separate the cases without and with B. bacilliformis anemia in the invasive stage [34]: (*a*) In cases without anemia there are nonspecific symptoms, such as malaise, headache and occasional fever; in these cases diagnosis cannot be made at this stage of the disease unless blood cultures are secured. (*b*) B. bacilliformis anemia (synonyms: Oroya fever, fiebre grave de Carrión,[11] fiebre verrucosa de Guáitara [35]) is a febrile hemolytic anemia with bartonella organisms parasitizing the erythrocytes. It occurs infrequently during the invasive stage of Carrión's disease. It is interesting that in areas where the disease is endemic, the anemia is infrequent. At present, however, there is no statistical report available from these endemic areas indicating the exact incidence of B. bacilliformis anemia in Carrión's disease.

B. bacilliformis anemia has distinguishing clinical and hematologic features and develops so rapidly that it can be compared only with the

31. Weinman, D., and Pinkerton, H.: Carrion's Disease: IV. Natural Sources of Bartonella in the Endemic Zone, Proc. Soc. Exper. Biol. & Med. **37**:596-598, 1937.

32. Hurtado, A.: "Daniel A. Carrión," Report of an Address, Bol. informat. Asoc. med. Peruana **6**:261, 1939.

33. Ricketts, G.: Contribución al estudio cliníco de la enfermedad de Carrión, Thesis, Lima, 1942.

34. Ricketts, W. E.: Bartonella Bacilliformis Anemia (Oroya Fever): A Study of Thirty Cases, Blood **3**:1025, 1948.

35. (*a*) Patino Carmargo, L.: Bartonellosis en Colombia: Bartonellosis de Guáitara o fiebre verrucosa del Guáitara, Rev. Fac. de med., Bogotá **7**:467, 1939; (*b*) Un nouveau foyer de bartonellose en Amérique. Bull. Office internat. de'hyg. pub. **32**:570, 1940 (*c*) Patiño Carmargo, L.; Cifuentes, P., and Sánchez Herrera, M.: El primer caso de bartonellosis (fiebre verrucosa del Guáitara o verruga) en Bogotá, Bol. ofic. san. panam. **19**:1070, 1940. (*d*) Patiño Carmargo, L.: Estado actual de la bartonellosis (fiebre verrucosa, verruga) en el continente americano, Rev. Fac. de med., Bogotá **9**:160, 1940.

anemia occurring in an acute hemorrhage. This anemia occurs irrespective of age, sex or race.

The physical findings in the patients with severe anemia are rather dramatic and almost pathognomonic. The patients are deeply apathetic and have a peculiar discoloration of the skin and scleras due to the combination of slight icterus with very severe anemia. The conjunctivas and the matrixes of the nails are almost colorless and the ears almost transparent. The cardiovascular signs consist in tachycardia and soft hemic murmurs of varied intensity heard over the entire precordium; synchronously there are suprasternal, epigastric and carotid pulsations; the blood pressure is moderately hypotensive, and occasionally there is peripheral collapse. In contrast to previous reports, dyspnea at rest is very unusual in anemic patients without intercurrent infection,[36] even with erythrocyte counts below 1,000,000; in patients with some intercurrent infection, especially with salmonellosis, it is a constant finding.[37] Cough and expectoration with rhonchi and rales on physical examination early in the disease may simulate a primary infection of the upper respiratory tract. Headache, vertigo, restlessness and drowsiness, tinnitus, insomnia and occasionally angina pectoris are symptoms dependent on the intensity of the anemia. Patients often complain of a feeling of transmission of the cardiac impulse to the head and ears. Odriozola said, "The patient hears his murmurs."

Thirst and anorexia are common features. The tongue is usually dry with a coffee-brown coating. In the early stages of the anemia profuse sweating may occur, but later the skin becomes very dry, a significant point in the differentiation from malaria. There is a generalized lymphadenopathy with nontender lymph nodes of the size of a small bean without periadenitis. Enlarged lymph nodes occurred in all except 3 fatal cases. Enlargement of the spleen, which had been described as a constant finding,[38] appeared only in the cases with intercurrent infections in this series, thus confirming a previous report.[39]

Observations on the course and type of fever in the past have been varied and even contradictory.[40] Ordinarily after a variable onset with or without chills, the temperature fluctuates between 37.5 and 38.5

36. Hurtado, A.; Pons, J., and Merino, C.: La anemia en la enfermedad de Carrión o verruga peruana, An. Fac. med., Lima **21**:25, 1938. Odriozola.[11]

37. (*a*) Ricketts, W. E.: Intercurrent Infection of Carrion's Disease, Am. J. Trop. Med. **28**:437, 1948. (*b*) Odriozola.[11] (*c*) Barton.[13]

38. Odriozola.[11] Tamayo.[14] Castillo.[24]

39. Arce, J.: Apreciaciones generales sobre el diagnóstico y la clinica: La verruga peruana no genera esplenomegalia, An. Fac. med., Lima **7**:5, 1921.

40. (*a*) Mimbella, P. S.: La curva térmica de la enfermedad de Carrión, Crón. méd., Lima **14**:357, 1897. (*b*) Larrea y Quezada, A.: Contribución al estudio de la verruga peruana, ibid. **4**:391, 1887. (*c*) Odriozola.[11] (*d*) Tamayo.[14] (*e*) Antunez.[22] (*f*) Castillo.[24] (*g*) Arce.[23]

degrees C. (99.5 and 101.3 F.), but it may be higher or lower, and occasionally patients with severe anemia have an almost afebrile course. The severity of the anemia does not parallel the intensity of the fever, intermittent fever being due to concurrent malaria.[37a] Odriozola [11] observed that in many cases there was later a pronounced elevation of temperature, which he interpreted as prodromal to a second outbreak, or "hyperthermic" course. This elevation of temperature has been found [37a] to be associated with intercurrent infection, usually due to Salmonella organisms.

The hemorrhagic tendency may be manifested by petechiae, ecchymoses, epistaxis, gingival hemorrhage, hematemesis or melena. Petechial hemorrhages were mentioned in the first descriptions of the disease [41] and occurred in the martyr Carrión.[10a] Pinpoint hemorrhages were originally thought to be produced by the beginning eruption of verrugas [11] and the epistaxis supposedly produced by verrugas in the mucosa of the nose. This explanation was not satisfactory, for in most of the cases with epistaxis the bleeding occurred during the initial stage of the disease, when verrugas were not seen. Malo [42] first made this differentiation between the petechiae and the pinpoint verrugas in the skin. I [43] demonstrated in previous studies that in cases with purpura there is a constant thrombopenia.

Clouding of the sensorium and delirium are rather common.[44] In most anemic cases mental symptoms, such as irritability and insomnia, were of secondary importance; however, in other cases the mental symptoms constituted a real psychosis. Pierola [45] first described these psychotic episodes and considered them transitory and related to the course of the disease. Alterations of the memory and consciousness were found in a previous study [33] of 30 patients with B. bacilliformis anemia, 8 of whom had meningoencephalitic symptoms.[34]

As early as 1898, Tamayo [46] and Hercelles [47] described a fall in the erythrocyte count and in the hemoglobin values together with anisocy-

41. (*a*) Barton, A.: La enfermedad de Carrión y las infecciones similtíficas: Su diferenciación, Crón. méd., Lima **31**:37, 1914. (*b*) Manrique, E.: El problema terapéutico de la fiebre anemizante grave de Carrión, Reforma méd., Lima **23**:681, 683 and 694, 1937. (*c*) Landauro, A.: Complicaciones de los enfermos de verruga peruana, Crón. méd., Lima **54**:46, 1937. Odriozola.[11]

42. Malo, N.: Verruga peruana Thesis, Santiago, 1852; Crón. méd., Lima **23**: 295, 1906.

43. Footnotes 33 and 34.

44. Valdizan, H.: El delirio de la enfermedad de Carrión, Crón. méd., Lima **36**:263, 1919. Ricketts.[33]

45. Pierola, L. O.: Vesania verrucosa, Crón. méd., Lima **20**:305, 1903.

46. Tamayo, M. O.: Hematología de la enfermedad de Carrión, Crón. méd., Lima **15**:337, 1898.

47. Hercelles, O.: Ligeros apuntes sobre la histología patológica de la verruga peruana, Crón. méd., Lima **17**:353 and 369, 1900; **18**:3 and 17, 1901.

tosis and poikilocytosis. Since then, many hematologic studies have been made in B. bacilliformis anemia,[48] including a very complete monograph by Hurtado, Pons and Merino.[36] The anemia is macrocytic and usually hypochromic, and the erythrocyte count may drop as low as 500,000 in the first two to four weeks of illness. The hematocrit reading decreases proportionally to the fall in the erythrocytes. The peripheral blood shows marked regenerative activity of both erythroid and myeloid series, and the number of nucleated red cells may be exceedingly high. In a previous paper [34] a case was reported in which there were 20 erythroblasts and 461 normoblasts to each 100 leukocytes, or 37,164 normoblasts per cubic millimeter. Frequently refractile basophil granulations, nuclear particles, Howell-Jolly bodies, polychromasia, poikylocytosis and anisocytosis are found in the erythrocytes. Reticulocytes may increase to 50 per cent.

The pathognomonic sign of the disease in the erythrocyte is the organism B. bacilliformis. This organism is very polymorphic. In Giemsa staining it appears as though red-violet rods are situated on the red cells, and the "bacilliform" bodies may be as numerous as 20 on each erythrocyte in heavy infections (fig. 1). The length of the organism varies from 1 to 3 microns and the width from 0.25 to 0.50 micron. They are distributed in rods in a Y, V or chain appearance and they may be curved or show polar enlargement.[17] These organisms are well stained by the May-Grunwald-Giemsa method or by any of the modifications of the Romanowski method. As to the relation of the bartonellas to the red cells, which has been a controversial point, modern studies [49]

(48) (*a*) Arce, J.: La anemia de la fibre grave de Carrión; Estudio comparado con otras anemias; Su mecanismo, Actas y trab. d. V. Cong. lat. am. med. **5**:22, 1914. (*b*) Napanga, J.: El hemograma de Schilling en la enfermedad de Carrión, Thesis, Lima, 1938. (*c*) Gastiaburu, J. C., and Rebagliati, R.: Sobre la hematología: La etiología de la enfermedad de Carrión, Crón. méd., Lima **26**:377, 1909. (*d*) Barton, A.: Descripción de elementas endo-globulares hallados en los enfermos de fiebre verrucosa, ibid. **26**:7, 1909. (*e*) Monge, C.: Algunos apuntes sobre la hematología de la "enfermedad de Carrión," Thesis, Lima, 1910; ibid. **27**:297, 317 and 326, 1910. (*f*) Rebagliati, R.: Los cuerpos de Barton, ibid. **32**:36, 1915; Reforma méd., Lima **1**:5, 1915. (*g*) Weiss, P.: Contribucion al estudio de la verruga peruana o enfermedad de Carrión, Rev. méd. latino-am. **18**:1121, 1933. (*h*) Carvallo, J.: La médula ósea en la enfermedad de Carrión, Thesis, Lima, 1910; Crón. méd., Lima **28**:34, 42, 57, 78, 85, 110, 120 and 135, 1911. (*i*) Hercelles, O.: Hematología de la enfermedad de Carrión, Actas y trab. d. V Cong. lat. am. Med. **2**:28-49, 1914. (*j*) Monge, C., and Weiss, P.: Sobre la hematología de la enfermedad de Carrión, An. Fac. med., Lima, 1927; Rev. sud.-am. de med. et de chir. **1**:570, 1930. (*k*) Tamayo, M. O.: Fisiología morbosa de los órganos hematopoyéticos en la enfermedad de Carrión, Crón. méd., Lima **16**:431, 1899. (*l*) Gastiaburu, J. C., and Rebagliati, R.: Sobre la hematología y la etiología de la enfermedad de Carrión, ibid. **26**:377, 1903.

49. Aldana, L. G.: La bacteriología de la enfermedad de Carrión, Rev. méd. peruana **46**:235, 1929.

tend to indicate that the bartonellas are not located within the red cells but are, rather, superimposed on them.

While leukocytosis has been described in this anemia,[50] a normal leukocytic count [36] or even a tendency toward leukopenia [48l] has also been

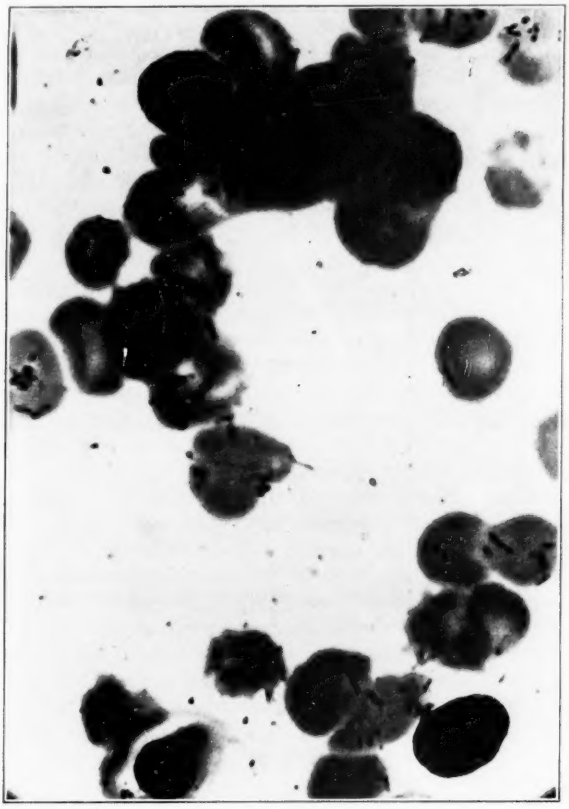

Fig. 1.—Massive parasitism of erythrocytes in the peripheral blood by B. bacilliformis. Bartonellas are present on the cells and outside the cells. Giemsa stain; × 2,200.

reported. In a previous study it was reported [34] that the leukocyte count varies in each case and in the same patient during the course of the

50. Weiss, P.: Hacia una concepción de la verruga peruana, Thesis, 1927; An. Fac. de med., Lima **9**:279, 1926. Larrea y Quezada.[40b] Monge and Weiss.[48l] Gastiaburu.[48l]

disease. Slight leukocytosis is not uncommon, but marked leukocytosis in cases without intercurrent infections is extremely rare. A very frequent finding is a shift to the left characterized by the presence of myeloblasts, myelocytes and metamyelocytes. The leukocyte count appears to be of value as an index to the course of the bartonella infection and in detecting intercurrent infections.

Thrombopenia has been found [33] in 8 cases with purpura and external hemorrhages. These hemorrhages were transitory and lasted no more than two weeks, being parallel to the drop in the platelet count.

The interaction between the bartonellas and the reticuloendothelial system has been studied extensively.[51] The bartonellas are found in large numbers in the phagocytic cells, such as the Kupffer cells of the liver, littoral cells of the spleen, and in the lymph nodes, indicating clearly that the activity of the bartonellas is centered in the reticuloendothelial system.

The term "critical stage" [48e] in B. bartonella anemia is applied to the period of transition in which the organism suddenly disappears from the red cells.[34] The mechanism of this change is not entirely understood, but within a few days the bartonellas may disappear from the peripheral erythrocytes. The hematologic signs of this transition are as follows: (*a*) a change in the form of the bartonellas from a bacilliform to a coccoid, originally described by Barton [12] as blurring of the outline of the organism, with the appearance of sphere, hourglass, pear shape or granule forms (these are the coccoid bartonellas); (*b*) a decrease in the number of parasitized erythrocytes and in the number of bartonellas on each erythrocyte; (*c*) an increase in the erythrocyte count (fig. 2); (*d*) a return to normal from the indirect hyperbilirubinemia; (*e*) an increase in the number of reticulocytes; (*f*) a decrease in the macrocytosis, the erythrocytes later in the disease regaining normal size, even having a tendency to microcytosis; (*g*) lymphocytosis and the reappearance of monocytes and eosinophils, and (*h*) in the leukocytes a shift of the polymorphonuclear series to the "right," a characteristic which persists during the rest of the disease. Clinically, corresponding with this transition, the fever disappears, the subicteric tinge of the skin and scleras disappears leaving an intense earthen gray pallor. With the

51. (*a*) Noguchi, H.: The Etiology of Oroya Fever: Pathological Changes in Animals Experimentally Infected with Bartonella Bacilliformis; Distribution of the Parasites in Tissues, J. Exper. Med. **45**:437, 1927. (*b*) Pinkerton, H., and Weinman, D.: Carrion's Disease: Comparative Morphology of the Etiological Agent in Oroya Fever and Verruga Peruviana, Proc. Soc. Exper. Biol. & Med. **37**:591, 1937; (*c*) Carrion's Disease: Behavior of the Etiological Agent Within Cells Growing or Surviving in Vitro, ibid. **37**:587, 1937. (*d*) Alzamora-Castro, V.: Enfermedad de Carrión: Un ensayo sobre patogenia, An. Fac. med., Lima **23**:9, 1940. (*e*) Mackehenie, D.: Mesenquime et maladie de Carrión, Rev. sud.-am. de méd. et de chir. **3**:326, 1932. (*f*) Footnote 26.

prompt rise in the number of erythrocytes, the symptoms of anemia, such as fainting, dizziness, tinnitus, etc., as well as the hemic heart murmurs, disappear, the blood pressure rises and the patient appears to be convalescing. However, this sequence of events does not always occur, for clinical improvement does not always parallel the disappearance of B.

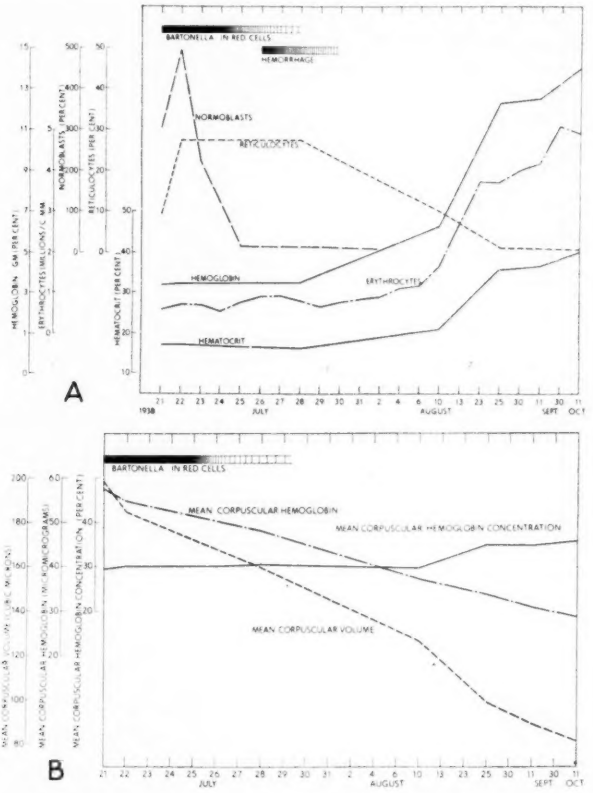

Fig. 2.—Recovery phase in a case of B. bacilliformis anemia. *A*, parallel increase of erythrocytes, hemoglobin and hematocrit values; *B*, mean corpuscular values, showing the striking fall in the mean corpuscular volume. The solid bar indicates a heavy concentration of B. bacilliformis; the progressively lighter shading indicates progressively diminishing numbers of parasites.

bacilliformis from the erythrocytes. There may be an increased severity of the clinical course of the disease, which is due to an atypical course of the disease itself or to the onset of intercurrent infections. It is not

known whether the bartonella infection itself is responsible for death in these cases.

Intercurrent infections may develop in these patients during the critical period of the anemia, when there appears to be a lowered resistance of the host to invading organisms harbored in the gastrointestinal tract.[37] These organisms frequently produce a fatal septicemia. In these cases the symptoms are bizarre and confusing. There is usually a rise in the temperature, tachycardia, diarrhea, dyspnea and psychomotor excitability, followed shortly by death. There is leukocytosis with shift to the left in the polymorphonuclear series and a fall in the number of reticulocytes and normoblasts. Blood cultures and examination of blood smears for malaria parasites are very helpful in determining the complicating organism.

B. bacilliformis anemia is a hemolytic anemia in which the destruction of erythrocytes is due to B. bacilliformis. The rate of destruction of the erythrocytes and the increased bilirubinema[36] are directly proportional to the number of parasitized erythrocytes. Hurtado, Pons and Merino[36] have shown that the fragility of the erythrocytes is normal in this disease. There are no spherocytes, and hemoglobinuria does not occur. Enlargement of the spleen is not demonstrable on physical examination in cases without intercurrent infections.[52]

An early suggestion was that the B.b.a. was "addisonian" anemia. Guzmán Barrón[53] demonstrated the presence of Castle's principle in the gastric secretion, and careful hematologic studies[36] have shown that the anemia is normoblastic and not megaloblastic and is accompanied by marked reticulocytosis. Histologically there is evidence of destruction of erythrocytes in the reticuloendothelial system, as the Kupffer cells, littoral cells of the spleen and lymph nodes and other phagocytes appear filled with bartonellas and erythrocytes (fig. 3).

3. *Preeruptive Stage.*—This stage, between the febrile anemia of the invasive stage and the eruption of verrugas, Odriozola[11] called "intermediate" and Weiss "preeruptive."[54] Many interesting clinical forms, such as phlebitis, pleuritis and encephalitis, occur chronologically between the invasive and eruptive stages but are unrelated to the anemia or to the eruption of verrugas.

This stage is usually not accompanied with fever, except when manifestations of the disease such as phlebitis and erythema[55] produce it.

52. Ricketts.[34] Mimbella.[40a]

53. Guzmán Barrón, A.: La reaccion de Van den Bergh, hemoaglutininas y hemolisinas en la enfermedad de Carrión, Crón. méd., Lima **43**:79, 1926.

54. Weiss, P.: Contribución al estudio de la verruga peruana o enfermedad de Carrión, Rev. méd. latino-am. **18**:1121, 1933. Footnote 48.

55. Ricketts, R., and de Guillermo, C.: Reaccion de tipo eritematoide en el periodo pre-eruptivo en un caso de enfermedad de Carrión, Rev. estud. med., Lima **3**:7, 1939.

Pain is one of the most constant and most frequent symptoms of the preeruptive stage. The pains are located in the bones, joints and muscles. When in the bones and joints, they are particularly in the forearms, wrists, feet, heels, elbow, shoulders and in the epiphyses of the long bones. The pains are transitory, lasting from a few minutes

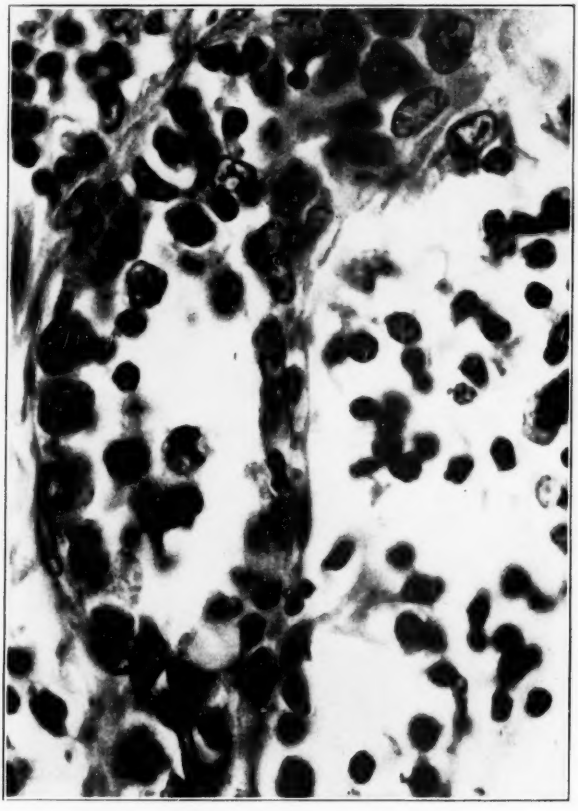

Fig. 3.—Large littoral cells lining the splenic sinus, with colony-like masses, each composed of innumerable bartonellas. Giemsa stain.

to two or three days, and the patients say they "jump" from one bone or group of bones to another. They can be very severe and are often accentuated at night or on exposure to cold but are rarely influenced by external pressure. Pains in joints can be very annoying, occurring with

slight or no local evidence of inflammation. The pain in the muscles is transitory and changeable, appearing most frequently in the muscles of the back of the neck, deltoid, gastrocnemius and sternocleidomastoid muscles,[33] but it is rarely of marked intensity. The pains do not respond to salicylates. Cramps are not infrequent.

Fig. 4.—*A*, nodular facial verrugas with blood oozing from the lesion over the right eyebrow. *B*, multiple verrugas of varying sizes on the left upper extremities spreading over the extensor surfaces of the hands and arms. *C*, multiple confluent small verrugas on the dorsa of the hands. *D*, similar lesions about the elbows.

Cases with pains in the bones, joints, tendons, or muscles were described in the last century as "rheumatoid types" of the disease.[56]

56. Medina and others.[10a] Odriozola.[11]

There are instances in which the differential diagnosis has challenged the diagnostic acumen of the best clinicians, being mislabeled as "rheumatic disease," "brucellosis" or other similar conditions, until the appearance of verrugas led to the correct diagnosis. Kuczinsky [25] inter-

Fig. 5.—Unusually numerous verrugas on the skin of the legs; *A*, anterior view; *B*, posterior view. *C* and *D*, regression of verrugas two months later.

preted such pains as "verrucous rheumatism" due to the toxic activity of B. bacilliformis.

Paresthesias and abnormal sensations are common. Some of the patients described their sensations as "numbness," "ants walking over the skin," "burning of the skin," most often in the palms and soles,

"running electric shots" and "needles in the skin." Pruritus is often present, usually mild and transient, and often disappearing before the eruption of verrugas.

The hematologic findings during this period are as follows: The number of erythrocytes becomes normal in those patients who had been anemic, and no immature cells such as reticulocytes or normoblasts are observed in the peripheral blood, nor the bartonellas to be found. Microcytosis was described by Hercelles [47] in 1900. There is neutropenia without evidence of immature elements; the eosinophils are normal, although an eosinophilic state has been described.[54] The monocytes are normal in number or slightly increased and there is marked

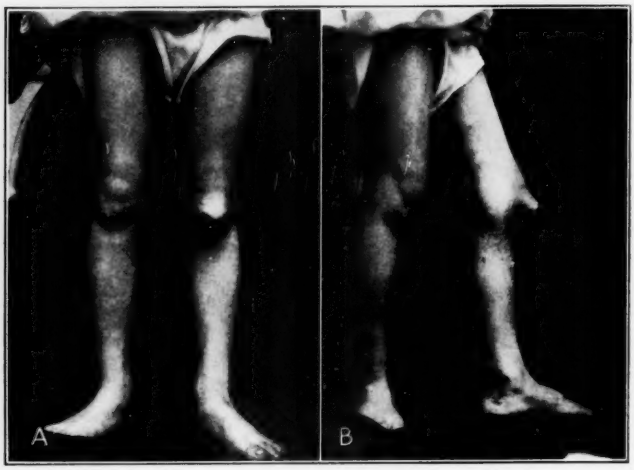

Fig. 6.—Protruding nodular verrugas of so-called mule type in lateral (*A*) and anterior (*B*) views.

increase in lymphocytes, occasionally up to 60 and 70 per cent. The number of white cells is normal, or there is a tendency toward leukopenia.

The lymphadenopathy occurring during the invasive stage disappears. Splenomegaly in noncomplicated cases occurs very rarely [33] but in cases with intercurrent infection is a constant finding.[37a]

4. *Eruptive Stage.*—The appearance of red cutaneous nodules, "the verrugas," constitutes the external pathognomonic sign of the disease. They were known for many centuries, and there was a term for them in the Quechua dialect of the Peruvian Indians.[57] A well developed and generalized eruption of verrugas, varying in color from red to purple,

57. Vargas-Fano.[5] Matto.[6]

has distinctive characteristics unmistakable for any other disease (figs. 4 to 7). Usually several months elapse from the time of the infection until the appearance of verrugas. The nodules are situated most frequently on the uncovered parts of the body and dorsal surface of the extremities but may affect the skin in other regions.

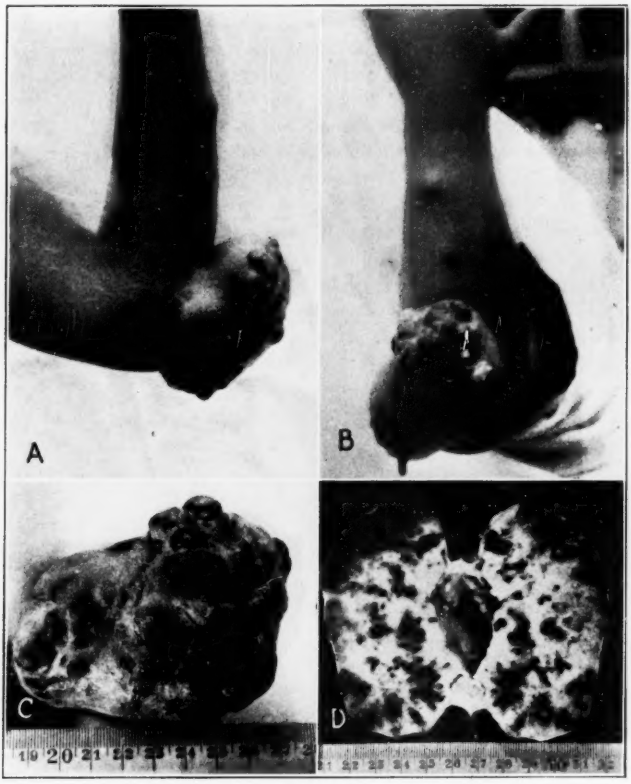

Fig. 7.—Enormous verruga studded with small verrugas on the elbow of an 11 year old boy. *A*, lateral view; *B*, dorsal view; *C*, dorsal aspect after resection; *D*, cut surface, demonstrating hemorrhages related to angiomatous areas.

The verrugas can be separated according to number, localization, evolution, shape, situation, size, disposition and general aspect of the eruption. They may be seen either in growth or in regression, the two stages sometimes coexisting in different verrugas in the same patient. The first clinical sign is a round, soft red papule no larger than a pin-

point that grows very rapidly in a few days or weeks. At this time it has passed from the histiocytic to the angiocytic phase. The vascularity of the nodule is easily seen upon pressure. Later they become as large as a walnut or a pear or larger. Occasionally the covering membrane is so thin that the nodule is an intense brilliant red. The florid eruption has in general been associated with a good prognosis.[11]

The growing verrugas may in the beginning appear as very small vesicles, mimicking the aspect of a common sudamen. Later a red point appears in the center corresponding to a verruga in formation, a form carefully studied by Carrión [10a] and later by others.[40] Mackehenie and Jimenez [58] found the specific organisms in the phlyctenular vesicles. These may become secondarily infected, resulting in a pustular form. The complete development of each nodule takes from thirty to sixty days, remaining stationary for a variable time. Salazar reported that the eruption of verrugas usually lasts from three months to one year.[59]

Many studies have been made on the histopathology of the verrucous nodes.[60] Mackehenie [60k] recognized a preeruptive histiocytic stage, an angioma-like, or angiocytic, stage and a sclerosing, or fibrocytic, stage. At the height of its development the verruga may resemble a cavernous angioma or very vascular granulation tissue. Strong [17] and associates found that the typical histologic features of a verruga consist in numerous new-formed small vessels, proliferated endothelial cells and the presence of bartonellas.

The verrugas have various shapes: round, pedunculated, sessile, etc. They may be in the skin, in subcutaneous tissue or even in deeper tissue and can originate in any mesenchymal tissue. Old descriptions of the

58. Mackehenie, D., and Jimenez-Franco, J.: Acerca del mosaico de poderes de la Bartonella bacilliformis, Reforma med., Lima **21**:677, 1935.

59. Salazar, T.: Historia de las verrugas, Thesis, Lima, 1858; Gac. med. de Lima **2**:161 and 175, 1858.

60. (*a*) Mayer, Rocha-Lima and Werner.[16a] (*b*) Strong.[17] (*c*) Mackehenie.[26] (*d*) Hercelles.[47] (*e*) Noguchi.[51a] (*f*) Mackehenie.[51e] (*g*) Velez, A.: De las verrugas, Thesis, Lima, 1861. (*h*) Izquierdo, V.: Spaltpilze bei der "Verruga peruana," Arch. f. path. Anat. **99**:411, 1885. (*i*) Tamayo, M. C.: Histología patológica de la verruga nodular, Thesis, Lima, 1899. (*j*) Escomel, E.: Anatomie pathologique du verrucome de Carrión, Ann. de dermat. et syph. **3**:961, 1902; Crón. méd., Lima **20**:51, 1903. (*k*) Mackehenie, D.: Estudio del noduloma verrucoso, Reforma méd., Lima **24**:50, 1938. (*l*) da Rocha Lima, H.: Zur Histologie der Verruga peruviana, Verhandl. d. deutsch. path. Gesellsch. **16**:409, 1913. (*m*) Cole, H. N., Verruga Peruviana and Its Comparative Study in Man and in the Ape, Arch. Int. Med. **10**:668 (Dec.) 1912; J. Cutan. Dis. **31**:384, 1913. (*n*) Noguchi, H.: Etiology of Oroya Fever: Bacterium peruvianum n. sp. Secondary Invader of Lesions of Verruga Peruviana, J. Exper. Med. **17**:165, 1928. (*o*) da Rocha, Lima, H.: Verruga peruviana und teleangiektatische Granulome, Arch. f. Schiffs.- u. Tropen-Hyg. **29**:525, 1925. (*p*) Letulle, M.: Histologie pathologique des veruges cutanées, cited by Odriozola,[11] p. 201.

disease [11] referred to the small nodes as "miliary" verrugas, nodular or "tuberculous" verrugas, because of their resemblance to the tubercles (figs. 4 and 5). The larger ones were called "mule type" (fig. 6) or "tumorous type" (fig. 7). In an 11 year old boy a verruga the size of a fist developed in the subcutaneous tissue of the elbow. From this tumor continuously drained serous fluid and blood until it was removed surgically. It appeared to be a very vascular angiomatous tumor, weighing 187 Gm. and studded with small verrugas.[61]

When located in the subcutaneous tissue, the verrugas may be adherent to other tissues, such as the aponeurosis, tendons and periosteum. The subcutaneous nodules have a tendency to push out the

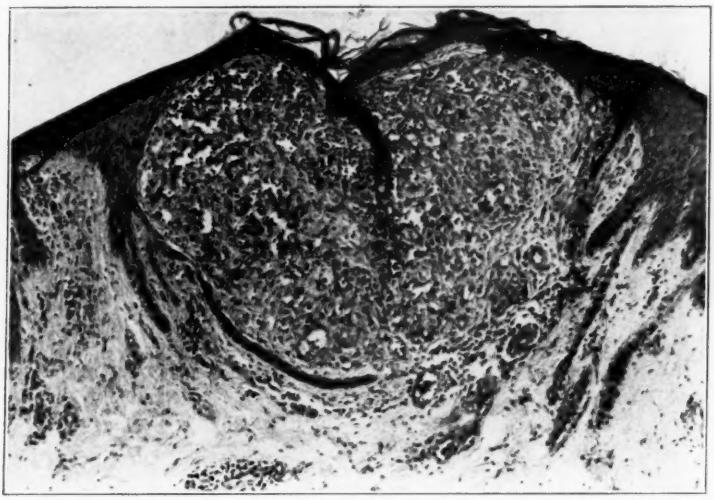

Fig. 8.—Small verruga, showing angiomatous features and perivascular infiltrates. Hematoxylin and eosin; × 155.

skin, making it thin and of a purplish color. The large verrugas may have a pedicle (fig. 9), partially or totally covered by the skin, and may be isolated or in conglomerates. In figure 5 there are illustrations of a patient who had a diffuse eruption of verrugas in the extremities and face. There were 1,873 verrugas on the right leg and right foot alone.

Localization of verrugas in the bones has been reported in the last century [62] and recently.[63] It occurred in 3 cases personally

61. Jimenez-Franco, cited by Ricketts,[85d] p. 112.

62. Tschudi.[8] Tupper.[21]

63. Arellano, A.: Primer caso clínico de localización ósea de verruga infecciosa, Crón. méd., Lima **12**:43, 1895.

studied.[33] They have also been reported in articular and periarticular cartilages [64]; in the muscles [64]; in the adventitia of the vessels [64]; in the mucosa of the mouth,[65] respiratory tract,[10a] esophagus and stomach [64]; in the vaginal serosas [66]; in the testis [66]; in the capsule of the kidney, and in the epididymis.[66] They have been described

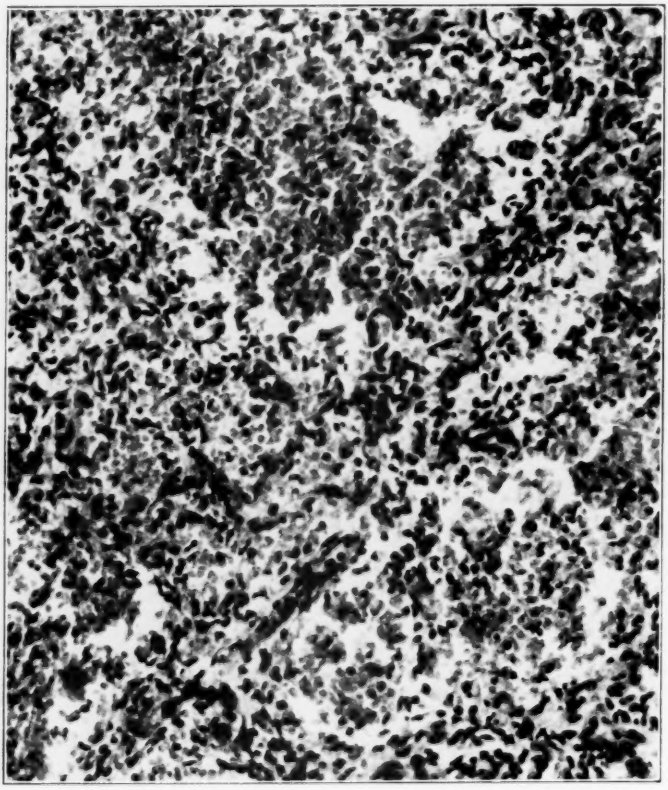

Fig. 9.—Section of large infected verruga, showing cavernous blood spaces. Hematoxylin and eosin; × 300.

64. Campodónico, E.: Caso interesante de verruga peruana ó verruga infecciosa, Crón. méd., Lima **12**:43, 1895.

65. Medina.[10a] Odriozola.[11] Campodónico.[64]

66. Delgado, L. M.: El brote de verruga en la vejiga, Rev. méd. peruana **7**:91-98, 1935.

in the lung,[64] heart,[67] liver and spleen,[64] in several reports on glands [64] and in the brain.[68] Many of the supposedly internal verrugas reported in these studies have been unaccompanied with histologic studies, a point which was emphasized by Arce.[23] It is possible that many of these internal nodules described did not represent bartonella granulomas but other types of lesions.

The verrugas themselves are nontender. Depending on the location of verrugas, varied symptoms may occur; for instance, if the verrugas are located in either of the bronchi, hemoptysis may occur; if in the brain, epileptic seizures. There is no correlation between the size of the verrugas and the local symptoms.

In the regressive stage they progressively become paler because of decreased vacularization of the nodule.[60k] This represents the transition from the angioblastic to the fibroblastic stage.[60k] Occasionally they become horny, covered with a thick crust (fig. 5 *C* and *D*). Tearing of the membrane of the node is followed by external hemorrhage. The verrugas in the skin may leave transitorily a central hypopigmented zone, surrounded by an area of hyperpigmentation. Scars are not found.[33] The regression of the node is more rapid if hemorrhage, thrombosis or infection occurs within the verrugas.[33] Infections of the verrucous nodes may occur focally or in systemic infections. The last is hematogenous, and usually numerous nodes suppurate at the same time; Salmonella organisms have been isolated from these infected nodules since early in this century,[69] and Noguchi found a bacterium which he named Bacterium peruvianum.[70]

Except for pains in the joints, muscles and bones, the eruption of cutaneous verrugas is accompanied only with local symptoms. Numerous general symptoms, such as fever, anemia, splenomegaly and hepatomegaly, previously pointed out as occurring in the eruptive stage, are due to secondary intercurrent infections. Symptoms that are present preeruptively may change abruptly with the eruption diminishing or disappearing; and the pains in the bones, joints and muscles will fade and sometimes disappear entirely. The eruption of verrugas occurs most frequently without anemia; however, in complicated cases with intercurrent infections [33] there may be anemia of varied intensity. In previous studies [43] 3 cases were reported with a polycythemic erythrocyte count, above 6,000,000 red cells and in 1 case 7,000,000.

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67. Odriozola.[11] Campodónico.[64]

68. González Olaechea, M.: Un caso de verruga infecciosa visceral, Crón. méd., Lima **7**:324, 1890.

69. Biffi, U., and Carbajal, G.: Sobre un caso de enfermedad de Carrión con nodulomas supurados, Crón. méd., Lima **21**:285, 1904.

70. Noguchi, H.: Etiology of Oroya Fever: IX. Bacterium Peruvianum n. sp.: A Secondary Invader of the Lesions of Verruga Peruana, J. Exper. Med. **47**:165, 1928.

Lymph nodes are not enlarged except as the result of infection of the node by the organism. Under these conditions the lymph nodes may become hard, tender and tumefacient, and occasionally there is a suppurative adenitis.

"RELAPSES" OF B. BACILLIFORMIS ANEMIA AND CHRONIC VERRUGAS

Patients who have had B. bacilliformis may later have a recurrence of symptoms with anemias one of the features. These relapses have been interpreted as relapses of the bartonella anemia, but they are, in fact, complications of several types. In these cases, B. bacilliformis is not found on the circulating erythrocytes. The hematologic characteristics of these secondary anemias are varied. The low erythrocyte count may be due to several factors: external hemorrhages, thrombocytopenic purpura, malaria, secondary infections and miscellaneous intercurrent infections.

Malo [71] in 1852 first described the reappearance of symptoms in patients with verrugas, attributing them to the invasion of the viscera. Odriozola [11] made the same correlation, emphasizing the change in the appearance of the verrugas in these cases; "the eruption gets pale, atrophic and disappears rapidly." After the isolation of the causative bacteria by Barton [13] in 1909, the recurrences associated with a high mortality were interpreted differently. It was thought that the "grave fever of Carrión" could reappear at any moment during the course of the disease,[11] an idea that has prevailed until today. The recurrence of anemia in Carrión's disease is said to be due to reinvasion of the blood by B. bacilliformis [54]; however, no proof of such reinvasion in man has ever been offered. Experimentally, reinvasion of the red cells occurs frequently in splenectomized animals.[72] Reinvasion of the red cells

71. Malo, N.: Thesis, Santiago, 1852, Crón. méd., Lima **13**:201, 1895.

72. Weinman, D.: Infectious Anemias Due to Bartonella and Related Red Cell Parasites, Tr. Am. Philos. Soc., 1944, vol. 32, pt. 3. Levi, M., and Chiodi, V.: Bartonella Anemias: Effects of Splenectomy on Structure of Erythrocytes in Rana Esculenta, Sperimentale, Arch. di biol. **88**:73, 1934. Perla, D.: Compensatory Changes Following Splenectomy in Bartonella Free Rats, Proc. Soc. Exper. Biol. & Med. **31**:983, 1934. Domagk, G., and Kikuth, W.: Development of Splenic Tissue in Liver of Sponenectomized Rats and Mice as Described by M. B. Schmidt: Relation to Bartonella Infection, Centralbl. f. allg. Path. v. path. Anat. **59**:1, 1933. Alsted, G.: Fate of Bartonella in Rats After Cessation of Anemia Following Splenectomy, Ztschr. f. Immunitätsforsch. u. exper. Therap. **80**:411, 1933; Hospitalstid. **76**:984, 1933. McCluskie, J. A. M., and Niven, J. S. F.: Blood Changes in Rats and Mice After Splenectomy, J. Path. & Bact. **39**:185, 1934. Colichon-Arbulu, H.: Infectiones espontáneas y provocadas en ratas en Lima, Rev. méd. peruana **6**:1611, 1934. Rhoads, C. P., and Muller, D. K.: Asso-

during the eruption of verrugas would not be immunologically feasible, for bartonella anemia occurs during the invasive stage, when the immune defenses are poor, and the eruption occurs when there is a marked immunologic defense. The cases with eruption of verrugas and with a febrile anemia are probably due to intercurrent complications, such as typhoid, salmonellae infections, malaria, amebiasis, etc., as was discussed in previous papers.[73]

Carrión's disease usually confers immunity for a lifetime. Dounon [74] in 1871 asserted that the disease occurred only once. Tschudi [8a] said that once it occurred there was a predisposition to reacquire it. Tupper,[21] for the first time, differentiated the recurrence of the disease from the

ciation of Bartonella Bodies with Induced Anemia in Dogs, J. Exper. Med. **61**:139, 1935. Knutti, R. E., and Hawkins, W. B.: Bartonella Incidence in Splenectomized Bile Fistula Dogs, ibid. **61**:115, 1935. Schwetz, J.: Sur eperythrozoon coccoides: Sur des infections mixtes à Eperythrozoon coccoides et à Bartonella muris, et sur des formes bizarres et énigmatiques trouvées chez les rats et les souris sauvages de Stanleyville, Compt. rend. Soc. de biol. **105**:408, 1934. Bacigalupo, J.: Efecto de la esplenectomia sobre las bartonellas de la sangre en rats, Actas. Cong. nac. med. **3**:943, 1934. Munch, O. O.: Bartonella Canis Infection in Relation to Secondary Anemia and the Associated Underlying Lesions, Am. J. M. Sc. **191**:388, 1936. Marschall, F.: Hämoglobinurie und Nierenveränderungen bei Bartonellenanämie entmilzter Ratten und bei Affenmalaria in ihrer Beziehung zum menschlichen Schwarzwasserfieber, Arch. f. Schiffs- u. Tropen-Hyg. **40**:151, 1936. Goyanes, J.: Aspects morphologiques de Bartonella canis, Ann. de parasitol. **14**:423, 1936. Lourau, M.; de Sacy, G. S., and Arthus, A.: Caractères des anémies à Bartonella muris, Compt. rend. Soc. de biol. **127**:1173, 1938. Lourau, M., Sacy, G. S., and Arthus, A.: L'anémie à Bartonella muris: caractères et évolution; Action des facteurs hépatiques antianémiques, Sang **13**:749, 1939. Alsted, G.: Studies on Immunity in Bartonella Anæmia, Acta path. et microbiol. Scandinav., 1938, supp. 37, p. 37. Lawkowicz, W.: Research on Bartonella Muris: Cultivation of the Organism in Vitro, Acta Convent. tertii de trop. atque malar. morbis **1**:577, 1938. Weiss, P.: Contribucion al estudio comparado de las bartonellas, Rev. méd. peruana **13**:116, 1941. Lawowicz, W.: Recherches expérimentelles sur Bartonella muris (note préliminaire), Bull. Office internat. d'hyg. pub. **30**:1781, 1938. Weinman, D., and Pinkerton, H. A.: Bartonella of the Guinea-Pig: Bartonella Tyzzeri Sp. Nov., Ann. Trop. Med. **32**:215, 1938. Kessler, W. R.: Studies on Experimental Bartonella Muris Anemia in the Albino Rat: II. Latent Infection and Resistance, Jr. Infect. Dis. **73**:65 and 77, 1943. Carr, D. T., and Essex, H. E.: Bartonellosis: Cause of Severe Anemia in Splenectomized Dogs, Proc. Soc. Exper. Biol. & Med. **57**:44, 1944. Malo.[71]

73. (*a*) Arce, J.: Algunas consideraciones sobre las infecciones microbianas que complican y agravan la fiebre grave de Carrión, Crón. méd., Lima **30**:501, 1913. (*b*) Tamayo, M. O.: Un ensayo de clasificación de los similtificos de la verruga peruana, ibid. **23**:295, 1906. (*c*) Jimenez-Franco, J.: Mortalidad e interferencias en la enfermedad de Carrión, Thesis, Lima, 1938. (*d*) Footnotes 33, 34, 35*a*, 41*a*.

74. Dounon, P. L. V.: Étude sur la verruga, maladie endémique dans les Andes péruviennes, Arch. de méd. nav. **16**:255, 1871.

frequent eruption of verrugas in nonimmunized patients. Carrión [10a] mentioned the chronic forms, and Antunez [22] described such forms as are frequent in the areas where the disease is endemic. I have studied cases in which a complete immunity did not occur,[33] as in 1 in which eruptions occurred three times in a ten year period. González Olaechea [75] had another patient who acquired Carrión's disease and soon after remained in a place where the disease was not present. Every year for twelve successive years he had an eruption of verrugas in the skin.

BARTONELLA REACTIONS INDEPENDENT OF THE ERUPTION OF VERRUGAS

Inflammatory reactions localized in different tissues, such as erythemas, phlebitis, parotitis and encephalitis, are seen most frequently in the preeruptive stage of the disease.[33] An erythema nodosum has been reported,[55] and Mackehenie found specific bartonella inflammations of the sebaceous follicles of the skin.[26]

Phlebitis.—Phlebitis in Carrión's disease is rather uncommon. It occurred in 5 out of 105 hospitalized patients, in incidence of 4.7 per cent.[33] Few authors [76] have referred to the involvement of the veins in this disease. Tupper [21] in 1887 described varicose veins of the leg and considered them as sequelae of the infection. Many cases have undoubtedly been misdiagnosed, as 1 labeled thrombosis of all four extremities.[54] In a report of 3 cases, the distinctive characteristics of the phlebitis were analyzed.[77] The general condition of the patients was found unaltered, and the conditions observed on physical examination were normal except in the areas with involved veins. There was a moderate irregular temperature oscillating between 37.5 and 38.5 C. (99.5 and 101.3 F.), without chills and with increased pulse rate. Initially, there is local perivenous inflammatory tumefaction, edema and increased temperature, but no lymphangitis or local lymphadenopathy occurred. After a few days to two weeks the perivenous inflammation appeared as a hard enlarged cordlike vein. There was no tendency toward invasive spreading or embolism; however, the phlebitis is frequently multiple. In all 3 cases blood cultures were positive for B. bacilliformis when Geiman's medium was used for culture.[28]

Inflammation of the Serous Membranes.—Any serous membrane, such as the pleura, pericardium and peritoneum, may exhibit nonsup-

75. González Olaechea, M.: Personal communication to the author.

76. Delgado-Bedoya, G.: Endoplebitis verrucosa, Rev. méd. peruana **13**:126, 1941. Rebagliati.[4] Tupper.[21] Larrea y Quezada.[40b] Weiss.[54]

77. Ricketts, W. E.: Phlebitis in Carrión's Disease: A Report of Three Cases, to be published.

purative changes. Pleuritis was described in the last century [11] and also later.[78] González Olaechea [79] demonstrated for the first time the presence of B. bacilliformis in the leukocytes and macrophages of the pleural effusion. The effusion is present in moderate amounts, as in 1 case in which 400 cc. was removed. However, clinical and pathologic evidence indicates that the effusion is due to a generalized serous inflammatory reaction and not to an internal verrugal node.

Parotitis.—Parotitis is quite rare, Manrique [41b] having described 1 case and I another, which persisted for about one month. Other inflammatory reactions have also been described, such as epididymitis [66] and iritis.[80]

MENTAL AND NERVOUS SYMPTOMS

Nervous Symptomatology.—Nervous and mental symptoms are not uncommon and have been attributed to neurotropic affinities of B. bacilliformis and explained on the basis of the neurologic lesions. In 1942, I attempted a classification of the nervous and mental forms of the disease.[33] This was followed by a similar study.[81] Mental and nervous symptoms are usually of secondary importance and represent a minimal part of the symptomatology; however, they can constitute the dominating picture, as occurred in 11 per cent out of a series of 105 cases [33] previously reported. The central and peripheral nervous system may be involved.[82]

Carrión suggested the possibility of localized meningeal verrugae. González Olaechea [68] described a verruga in the brain, and Campodónico [64] reported an autopsy case with verrugas in the meninges and choroid plexus. Mackehenie histopathologically proved the action of Bartonella on the nervous system,[83] and many other cases of such

78. Odriozola.[11] Jadassohn and Seiffert.[15] Arce.[39]

79. González Olaechea, M.: Proceso pleural verrucoso en el curso de una infeccion verrucoso, Rev. méd. puruana **5**:1331, 1933.

80. Del Carpio, G.: Iridociclitis en la enfermedad de Carrión, Thesis, Lima, 1935.

81. Lastres, J. B.: Las neurobartonellosis i; ensayo de interpretación etiopatogénica, Semana méd. **2**:871, 1943.

82. (*a*) Rossell, E.: Ligeros apuntes sobre la verruga peruana en el Callejon de Huailas, Actas y trab. d. V Cong. lat. am. med. **5**:198, 1914. (*b*) Antunez, D.: Distribucion geografica de la verruga peruana, ibid. **5**:191, 1914. (*c*) Odriozola.[11] (*d*) Monge, C., and Mackehenie, D.: Formas neurologicas de la enfermedad de Carrion, Crón. méd. **50**:123, 158 and 200, 1933.

83. (*a*) Mackehenie, D., and Encinas, E.: Acerca de un caso de verruga benigna complicado, Jorn. neuropsiquiat. Panamericana, **2**:306, 1939. (*b*) Mackehenie, D., and Alzamora, V.: Las lesiones anatómicas del sistema nervioso en la enfermeded de Carrión, Reforma méd., Lima **25**:419 and 438, 1939. (*c*) Monge and Mackehenie.[82d]

involvement have been reported.[84] Encinas showed alterations of the nervous structures as well as the meninges in 2 cases,[85] and Quiroga-Mena[86] referred to a possible diffuse encephalopathis.

Carrión was the first to describe meningeal symptoms.[10a] In several cases meningeal symptoms have developed during the invasive stage of the disease or during the crtical phase of the anemia. In 1 of the patients under my observation with massive parasitism of the red cells (96 per cent of the cells of the peripheral blood) and an anemia (nearly a half million red cells), the meningocephalic symptoms appeared as the last step in the progressive and fatal evolution of the bartonellosis. A case of polioencephalitis was reported by me[33] in 1942, and Monge and Mackehenie[82d] reported a choreic syndrome. Paresis is not uncommon.[87] In 1 case in my experience there was a transitory quadriparesis; in another a spastic paraplegia, and in a third epilepsy coinciding with the eruption of verrugas. Ortiz[87] described patients with neuralgias and paresias who bathed in natural thermal Peruvian springs (Chancos in Carhuas and Chilcas in Mancos, Ancash, Peru) with a definite improvement. I have reported a transitory paralysis of the fifth, ninth, tenth and eleventh cranial nerves before the eruption of verrugas.[33] In another case polyneuritis resulted in marked muscular atrophy of the extremities. Neuralgias and radicular pains are not uncommon. Localized hyperhidrosis is said to be due to lesions of the vegetative nervous system,[82d] and anatomopathologic changes in the vagus and sympathetic ganglions have also been reported.[83b]

Spinal Fluid.—There are very few studies on the spinal fluid in this disease.[88] In a previous analysis of 12 cases[33] with neurologic symptoms, the tensions of the spinal fluid were found normal or only slightly elevated; the fluid was transparent, alkaline in reaction without membrane formation and without coagulation. The results of the chemical

84. Bello, E.: Verruga peruana: Historia de un caso de enfermedad de Carrión, Crón. méd., Lima **10**:227, 1893. Lastres, J. B.: Complicaciones nerviosas de la verruga peruana, Rev. méd. peruana **6**:1690, 1934; Verruga peruana y poliomielitis anterior, ibid. **8**:771, 1936. Méndez P., and Anglas Quintana, P.: Síndrome de poliomielitis anterior aguda en el curso de la enfermedad de Carrión, Rev. neuro-psiquiat. **3**:88, 1940. Morales, A. L.: Un caso de enfermedad de Carrión con síndrome Parkinsoniano, Rev. méd. peruana **5**:646, 1933. Ricketts,[33] Mackehenie and Encinas.[83a] Mackehenie and Alzamora.[83b] Monge and Mackehenie.[82d]

85. Encinas, cited by Ricketts,[33] pt. 2, case reports, pp. 161 and 211.

86. Quiroga y Mena, R.: Verruga cerebral; Crón. méd., Lima 1899.

87. Ortiz, R.: La enfermedad de Carrión en el departamento de Ancash, Actas y. trab. d. V. cong. lat. am. med. **5**:648, 1914.

88. Lastres, J. B.: La cefalalgia en la verruga peruana, Rev. med. san mil., Lima **15**:11, 1942; El líquido céfalor-raquídeo en las neuro-bartonelosis, Gac. méd., Lima **1**:104, 1945. Ricketts,[33] Monge and Mackehenie.[82d]

determinations were variable. There was an increase in albumin in every patient with meningeal symptoms, in 1 the amount of albumin being 0.00230 Gm. per hundred cubic centimeters. The Pandy and Nonne-Appelt reactions were sometimes strongly positive. The amount of glucose in patients with meningeal symptoms may be slightly decreased and was found to be as low as 0.22 Gm. per hundred cubic centimeters in 1 case. The chlorides were not significantly lowered.

A cytologic study of the spinal fluid revealed that the cell count was normal, with the exception of cases with meningeal symptoms. In 1 case, there were 10.5 cells per cubic millimeter, predominantly lymphocytes, and in another, monocytes, lymphocytes, plasma cells and macrophages containing bartonellas. Guzman-Barron, cited by Monge and Mackehenie,[76d] was the first to demonstrate the presence of B. baccilliformis in the spinal fluid. In a previous study [33] the colloidal gold and mastic reactions were negative in 10 cases with nervous symptoms, although in one a paralytic precipitation was complete in all the tubes. Wassermann and Kahn reactions were negative in every case.

EDEMA

Edema, which was recorded in the earliest descriptions of the disease,[89] may be generalized or local. The former may be seen over the feet or in the face, simulating kidney disease; however, the urine is normal. The blood proteins in these cases are usually low, with an inversion of the albumin-globulin ratio. In 1 such case,[33] the total protein was 6.97 Gm. (albumin 2.36, globulin 4.61, with an albumin-globulin ratio of 0.51). Hurtado [36] referred the edema to the drop in the plasma albumin with resultant changes in the oncotic pressure of the blood. Merino [90] found during the acute stage of B. bacilliformis anemia a decrease in the amount of albumin proportional to the intensity of the anemia. He also observed that with the increase in red cells after the "critical stage" there was an increase in the amount of protein and globulin. The increase in the globulin protein fraction represents immunity against the bartonella infection.[90] After hemorrhage or protracted diarrhea, edema appears.

Localized edema in Carrión's disease without modification of the blood proteins is due to different factors, such as phlebitis, lymphatic obstruction in the vicinity of the verrugas, especially when subcutaneous nodes reach a fairly good size. Low plasma protein with an inverted albumin-globulin ratio of 0.56 in the blood coexisted in 1 case with a slight phlebitis of the saphenous vein and marked edema of the entire lower extremity.

89. Matto.[6] Mackehenie.[26]

90. Merino, C.: Las seroproteinas en la enfermedad de Carrión, Thesis, Lima, 1939.

PROGNOSIS

The prognosis in Carrión's disease varies considerably from patient to patient and in the different stages of the disease. The mortality occurring in B. bacilliformis anemia depends largely on the presence of intercurrent infections. Of 30 patients with such anemia, 9 died without demonstrable intercurrent infection. Eleven out of 15 with intercurrent infection died, an incidence of 73 per cent. One additional patient died with a coincidental rheumatic heart disease. These findings confirm previous reports [91] which emphasize the importance of intercurrent infections in Carrión's disease. They occurred in 47 out of 105 cases and were responsible for death in two thirds of the fatal cases.[35a] Jimenez-Franco, cited by me,[79] in 25 cases with autopsy found only 1 which was apparently uncomplicated. Probably the lowered resistance of the host in cases with B. bacilliformis anemia predisposes to fatal infections due to invasion by organisms from the gastrointestinal tract. A similar situation seems to occur in the cases complicated by amebic colitis. Parasitic infestation of the gastrointestinal tract, other than Endameba histolytica, does not alter the course of the disease. Malaria, the most frequent intercurrent infection, did not significantly affect the immunobiologic course of Carrión's disease. The host's defenses against intercurrent infections are not decreased during the preeruptive or eruptive stage of the disease. Of 75 patients observed during the preeruptive and eruptive stages, only 3 died, 1 with an E. typhosa infection and 2 with tuberculous meningitis.

TREATMENT

Until recently there has been no specific therapeutic agent for Carrión's disease, the treatment being largely symptomatic. Penicillin has recently been reported as producing good results in halting the course of the bartonella anemia.[92] Streptomycin seems to have a similar action.[93] Further studies are, however, necessary to evaluate the action of these drugs in the disease.

A good deal of therapeutic effort has been directed toward stimulating the bone marrow in bartonella anemia. This is of dubious impor-

91. Ricketts.[33] Ricketts.[37a] Alazamora-Castro.[51d] Weinman.[72a] Jimenez-Franco.[73c] Hercelles, O.: Estudio de la bartonella en los organos y tejidos y deducciones que de el se sacan en el proceso anatomo-pathológico de la enfermedad, Rev. méd. peruana **7**:235, 1935.

92. Merino, C.: Efectos de la penicilina en un caso de fiebre grave de Carrión, Gac. méd., Lima **1**:8, 1944. Aldana, G. L., and Tisnado Munoz, S.: Penicilina y enfermedad de Carrión: Estudio experimental y clínicõ, Rev. méd. peruana **18**:343, 1945. Merino, C.: La penicilina en el tratamiento de la enfermedad de Carrión, ibid. **18**:329, 1945; J. Lab. & Clin. Med. **30**:1021, 1945.

93. Merino, C.: Personal communication to the author.

tance in cases without any complication, as the main problem is not to stimulate the formation of erythrocytes but to prevent the effects of their destruction. The reticulocytosis is evidence of active regeneration,[34] but it is not adequate to compensate for the extreme hemolysis. In the course of the favorable cases there is a sudden spontaneous transition with disappearance of the bartonellas from the erythrocytes. This phenomenon may give the fallacious impression that a particular drug or treatment is responsible for such change.

Blood transfusions appear to be indicated; however, up to the present they have rarely been used. This is due largely to the prevailing theory [50] that the disappearance of the bartonellas from the erythrocytes occurring during the "crisis" of the anemia is due to immunity of the red cells toward the bartonellas. Blood transfusions according to this theory will alter the immunity, since the donor cells are supposedly more susceptible and so are more apt to be parasitized. This theory is not acceptable, as the erythrocytes have never been known to have immunologic activity. The immunologic changes which occur in the host in the critical stage produce the changes both in the shape and in the clearance of the bartonellas from the erythrocytes. This is supported by the fact that the anemia does not recur in the course of the disease, even in fatal intercurrent infections occur. Small blood transfusions, 300 to 400 cc., which were available in only a few cases, proved, in my experience, to be a life-saving procedure.[33] It seems that the anemic patients with massive parasitism will greatly benefit from repeated blood transfusions as supportive therapy against the bartonella infection, the anemia and the frequent intercurrent infections. Transfusions are indicated only in this period, for when the bartonellas disappear from the erythrocytes, the destruction of red cells ceases and there is a spontaneous prompt recovery. A second therapeutic effort, such as the use of antibiotics, should be directed to prevent intercurrent infections which largely account for the high mortality in cases of B.b.a.

The treatment of the disease during the preeruptive and eruptive stages is merely symptomatic. Patients with numerous verrugas of the extremities may have to remain in bed. For many decades local applications of various drugs to the skin [94] and administration of infusions of various plants [95] were given to produce the eruption of the verrugas, which appear to be associated with a relative immunity of the host toward the bartonella infection. These measures, however, have never

94. Escomel, E.: La maladie de Carrión ou verruga du Perou: Les dernières acquisitions, Bull. Soc. path. exot. **22**:405, 1929. Weinman.[72a] Dounon.[74]

95. Maldonado, A.: El escenario de la enfermedad de Carrión en el valle de Santa Eulalia y algunos datos sobre los plebotomus que la transiten, Crón. méd., Lima **50**:385, 1933. Rebagliati.[4] Odriozola.[11]

been demonstrated to change the course of the infection. Large "mule" or "tumoral" verrugas may need to be removed surgically in some cases.

Immunologic therapy has not been found to be effective, nor has convalescent therapy given satisfactory results. Efforts were made, however, with immune serum from rabbits, which was administered to 3 patients with bartonella anemia, in 1942.[96] In 1 of these cases, which I had the privilege of following during the succeeding year, the course of the disease was not altered. Kuczinski [25] has properly emphasized the importance of the administration of vitamins B_1 and C in this disease.

SUMMARY

Carrión's disease and verruga peruviana are synonomous. The eponym honors Daniel Carrión, who, by self inoculation, established experimentally in 1885 the relationship between Bartonella bacilliformis anemia and the eruptive phase of this disease. Carrión's disease is caused by B. bacilliformis, a polymorphous organism classified as a bacterium, and is limited to certain zones of the Andes in Peru, Colombia and Ecuador. Clinically, it may be divided into several stages: incubative, invasive, preeruptive and eruptive with focal lesions called verrugas.

The length of the incubation period seems to vary from three to fourteen weeks, and the invasive stage varies with respect to symptoms, duration and prognosis. The onset may be insidious, with vague noncharacteristic symptoms, or it may be sudden, with chills, high fever, sweating, headache and occasional delirium. Sometimes symptoms are absent altogether.

Bartonella bacilliformis anemia (Oroya fever) is a febrile hemolytic anemia with distinguishing clinical and hematologic characteristic, occurring only rarely in the invasive stage. The anemia is macrocytic and frequently hypochromic, with signs of intense blood formation. The pathognomonic sign of the disease is the presence of B. bacilliformis on the erythrocytes. The anemia is normoblastic; there is no spherocytosis, and the saline fragility of the erythrocytes is normal. Histologically there is evidence of phagocytosis of erythrocyte in the cells of the reticuloendothelial system (the Kupffer cells and the cells lining the sinuses of the spleen and lymph nodes). There is a shift of the polymorphonuclear series to the left, characterized by the presence of myeloblasts, myelocytes and metamyelocytes. The bartonellas disappear from the erythrocytes in a very few days, and this is called the "critical stage" of the anemia. The hematologic changes of this transition are as follows: a change in the

96. Howe, C.: Studies on the Immunology of Carrión's Disease, Arch. Int. Med. **72**:147 (Aug.) 1943; Immune Serum Therapy in Oroya Fever, ibid. **72**:429 (Oct.) 1943.

shape of the bartonellas from the "bacilliform" to the "coccoid" form before complete clearance will take place, an increase in the erythrocyte count, reduction in the indirect hyperbilirubinemia to normal, increase in the number of monocytes and eosinophils and a "shift to the right" of the polymorphonuclear series. With the disappearance of the bartonellas from the erythrocytes, the symptoms due to the anemia vanish.

In the preeruptive stage, the symptoms are pains in the joints, muscles and bones; cramps, and paresthesias. Inflammatory reactions in various organs, such as erythemas, parotitis, phlebitis and encephalitis, occur most often in this stage. The bartonella infection may also involve the central or peripheral nervous system and the meninges.

The appearance of red cutaneous nodules, or verrugas, constitutes the pathognomonic objective clinical signs of the disease. These verrugas are usually located in the skin but may be situated in any mesenchymatous tissue. They are specific granulomas of various sizes, histologically typified by multiple newly formed small-calibered blood vessels, proliferating endothelial cells and bartonellas. Only rarely do these nodules produce local symptoms.

Carrión's disease usually confers immunity for a lifetime, although sometimes the immunity is only transitory.

The severity of the disease depends directly on the severity of the bartonella anemia, the poor prognosis being largely due to intercurrent infections of enteric origin. Until recently the treatment of this anemia has been entirely symptomatic. Preliminary studies appear to indicate that penicillin and streptomycin may halt the progress of the anemia. It is suggested that the prognosis may be improved by the use of adequate blood transfusions and the use of antibiotics.

HEPATITIS AND ITS SEQUELAE, INCLUDING THE DEVELOPMENT OF PORTAL CIRRHOSIS

Observations on One Hundred Cases

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THE PROBLEM of hepatitis has become a very real one since the onset of World War II. Just as in and after World War I, the incidence of hepatitis and perhaps the virulence of the icterogenic substance, which has definitely been shown to be a virus, have become greater.

Our observations are presented to bring out the following points:

1. That the virulence of the organism during the two years previous to this report has been great, especially when it has been transmitted by the infusion of plasma or blood.

2. That there is a correlation between the results of liver function tests and the clinical course of the disease.

3. That the physician should be alert concerning the possibility of homologous serum jaundice and of syringe-transmitted hepatitis.

4. That chronic hepatitis and portal cirrhosis do exist as sequelae of acute hepatitis.

From July 1946 through December 1948, 100 patients with hepatitis were observed. Data on the series presented were obtained largely from the Veterans Administration Hospital, Wood, Wis., but include reports on the cases of patients seen in a large general hospital (Milwaukee County Hospital) and privately.

From the Veterans Hospital, Wood, Wis., and the Marquette University School of Medicine.

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Incidence.—Of the 14,121 patients regularly admitted to the Veterans Administration Hospital during the period of this survey, 80 had hepatitis. This number represents an incidence of 0.56 per cent, which is comparable to that reported in other countries.[1]

Race and Sex Distribution.—Of the 100 patients, 98 were white and 2 were Negro; 86 were males and 14 were females. (The males predominated in the series simply because of the preponderance of males among veterans.)

Age Distribution.—The average age of the patients was 33; the youngest was 12, and the oldest was 84.

Duration of Illness.—The average course of acute hepatitis was two months, while that of chronic or recurrent hepatitis was six months to five years.

It is of epidemiologic importance to note that 3 of the patients studied were physicians, 4 were nurses, 3 were medical students and 2 were laboratory technicians. Seventeen patients were exposed to blood or blood products parenterally, and 7 were subjected to hypodermic injections within four months of the acute onset of illness. Five of the latter had diabetes.

Havens[2] stressed the virus etiology of hepatitis because of the following factors: (1) the failure of investigators to identify a causative bacteria; (2) the production of the disease in human volunteers by the ingestion of the filtrable agents, and (3) the early development of leukopenia similar to that seen in other viral infections. Two filtrable etiologic agents have been described. These icterogenic viruses differ in the length of the incubation period, in transmissibility and that they fail to demonstrate cross immunity. The high incidence of inoculation hepatitis associated with the high mortality rate in the present group of patients studied during the postwar period renders the means of transmission of considerable importance.

We have divided the forms of the disease into three main groups: (1) infectious hepatitis, including acute and chronic or recurrent forms; (2) inoculation hepatitis, due to infected homologous serum and syringe or needle transmitted, and (3) hepatitis complicating other illnesses.

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1. Stowman, K.: The Epidemic Outlook in Europe, J. A. M. A. **128**:185 (May 19) 1945.

2. Havens, W. P., Jr.: The Etiology of Infectious Hepatitis, J. A. M. A. **134**:653 (June 21) 1947.

Hepatitis may be caused by infectious agents other than icterogenic viruses.[3] The hepatitis associated with infectious mononucleosis and brucellosis was included in the study. Seventy-one per cent of the patients were in group 1, 24 per cent were in group 2, and the remaining 5 per cent were in group 3 (table 1).

The diagnosis of hepatitis is not difficult. In the ordinary acute attack, jaundice is the most arresting feature; this was true in 72 of our cases. A careful determination of a history of past episodes of icterus is important, particularly in cases of chronic or recurrent hepatic disease. Frequently a history of contact can be elicited. Questions directed to obtain a history of blood transfusions, plasma infusions, venipunctures, immunizations, blood counts and hypodermic medications often provide a lead to the diagnosis of inoculation hepatitis. The parenterally transmitted form of hepatitis has an average incubation

TABLE 1.—*Analysis of One Hundred Cases of Hepatitis*

Type of Hepatitis	Number of Cases	Number of Deaths	Mortality Rate, Percentage
Infectious hepatitis			
Acute	45	2	4.4
Chronic or recurrent	26	0	0
Inoculation hepatitis			
Due to infected homologous serum	17	7	41.2
Due to infected syringe or needle	7	1	14.3
Hepatitis associated with infectious mononucleosis	4	0	0
Hepatitis associated with brucellosis	1	0	0

period of sixty to one hundred and twenty days, whereas it is rare for the period in the spontaneously occurring type to exceed an interval of forty-five days following contact.[4]

A high percentage of the patients complained of digestive disturbances, such as anorexia, nausea, vomiting, postprandial distress and pain or distress in the right upper quadrant of the abdomen. General symptoms of malaise and easy fatigability were outstanding complaints.

3. (*a*) Capps, R. B.; Sborov, V., and Barker, M. H.: The Diagnosis of Infectious Hepatitis, J. A. M. A. **134**:595 (June 14) 1947. (*b*) DeMarsh, Q. B., and Alt, H. L.: Hepatitis Without Jaundice in Infectious Mononucleosis, Arch. Int. Med. **80**:257 (Aug.) 1947. (*c*) Gall, E. A.: Serum Phosphatase and Other Tests of Liver Function in Infectious Mononucleosis, Am. J. Clin. Path. **17**:529, 1947. (*d*) Abrams, H. L.: Infectious Mononucleosis with Intense Jaundice of Long Duration, New England J. Med. **238**:295, 1948. (*e*) Cohn, C., and Lidman, B. I.: Hepatitis Without Jaundice in Infectious Mononucleosis, J. Clin. Investigation **25**:145, 1946. (*f*) Morris, M. H.; Robbins, A., and Richter, E.: Acute Infectious Mononucleosis with Hepatitis: Presentation of Two Cases, New York State J. Med. **44**:1579, 1944.

4. Neefe, J. R.: Recent Advances in the Knowledge of "Virus Hepatitis," M. Clin. North America **30**:1407, 1946.

The incidence of physical findings related to the hepatic disease was as follows: jaundice, 72 per cent; hepatomegaly, 57 per cent, and splenomegaly in 12 per cent of the cases. Hepatic tenderness or pain in the lower right portion of the thorax on percussion was frequently encountered.

ACUTE INFECTIOUS HEPATITIS

The following case report illustrates acute infectious hepatitis with complete recovery.

CASE 1.—J. W. T., a white veteran and physician anesthetist of 29, entered the hospital on April 2, 1948 with complaints of nausea, vomiting, anorexia, epigastric distress, malaise, dark urine and jaundice of three days' duration. On physical examination, he did not appear acutely ill but was mildly icteric. The liver was palpably enlarged. The responses to laboratory tests ranged as follows: serum bilirubin, 0.4 to 9.4 mg. per hundred cubic centimeters; icterus index, 9 to 89; thymol turbidity, 3.6 to 8.3 units; prothrombin time, 60 to 100 per cent of normal; cephalin-cholesterol flocculation, 0 to 3 plus; cholesterol-cholesterol ester ratio, 144:60; intravenous hippuric acid, 0.6 to 1.1 Gm.; and two hour urinary urobilinogen, 0.3 to 3.7 Ehrlich units, and alkaline phosphatase, 7.3 to 13.6 Bodansky units per hundred cubic centimeters. The blood count, urinalysis, sedimentation rate and results of serodiagnosis were not remarkable. At the time of discharge, May 7, 1948, the patient's liver was no longer palpable, the jaundice had subsided, responses to all liver function tests had returned to normal and the patient was asymptomatic. After a few days of graduated activity, a follow-up profile of hepatic function remained within normal limits.

SYRINGE-TRANSMITTED OR NEEDLE-TRANSMITTED HEPATITIS

This form of hepatitis is no different from that classified as homologous serum hepatitis. It carries this designation because it has been proved that an inadequately sterilized syringe with multiple sterilized needles may transmit the icterogenic substance.

In our study of 100 patients there were 7 such instances, with a mortality rate of 14.3 per cent. This disease entity was first brought to public attention in 1943, when English physicians observed considerable increase in the number of cases of hepatitis among patients being treated for syphilis in venereal disease clinics.[5] When records were carefully checked, it was noted that the incidence had increased from about 1 per cent in 1933 to as high as 50 per cent in 1945. It had

5. (*a*) Role of Syringes in the Transmission of Jaundice, Special Articles, Lancet **2**:116, 1945. (*b*) Salaman, M. H.; Williams, D. I.; King, A. J., and Nicol, C. S.: Prevention of Jaundice Resulting from Antisyphilitic Treatment, ibid. **2**:7, 1944. (*c*) Darmady, E. M., and Hardwick, C.: Syringe-Transmitted Hepatitis, ibid. **2**:106, 1945. (*d*) Bigger, J. W.: Jaundice in Syphilitics Under Treatment, ibid. **1**:457, 1943.

been felt that the jaundice produced in these cases was due to the reaction to the arsenic given, but it is now obvious that in many cases it was most likely due to a transmitted virus of hepatocellular disease.[6]

Similar experiences have been encountered in arthritis and diabetes clinics and reported in the literature.[7] A recent report by Capps, Sborov and Scheifley [8] described the marked increase of hepatitis in a group of persons receiving tetanus toxoid intramuscularly. In our series, 5 patients who fell into this classification had diabetes and were attending the same diabetes clinic.

The reports to date indicate that adequate sterilization reduces the incidence of needle transmission. It has been shown that the icterogenic substance has an extreme resistance to the ordinary methods of sterilization.[5a] It has also been demonstrated that the virus is definitely inactivated or killed by sterilization with dry heat and that thirty to sixty minutes' boiling is probably effective. Individual needles and syringes should be utilized in the drawing of blood and in the parenteral administration of drugs. When all these measures were instituted in the diabetes clinic at the Veterans Administration Hosptial, the occurrence of syringe-transmitted hepatitis was entirely eliminated.

The following case report illustrates a form of inoculation hepatitis, apparently caused by an icterogenic agent transmitted by a syringe or needle and resulting in death.

Case 2.—C. C. M., a white veteran of 52, was admitted to the hospital Jan. 26, 1948 because of jaundice. He gave a history of having had diabetes, which was well controlled by diet and the administration of insulin, since 1936. He was a resident of an institution where he daily attended the diabetes clinic. An examination revealed generalized icterus and tenderness in the right upper quadrant of the abdomen, but the liver was not palpable. The range of laboratory values was as follows: serum bilirubin, 17.4 to 25 mg. per hundred cubic centimeters; icterus index, 57; immediate van den Bergh reaction, positive; two hour urinary urobilinogen, 1.0 Ehrlich unit per cubic centimeter; thymol turbidity, 16.7 to 19.6 units; cephalin-cholesterol flocculation, 2 to 4 plus; intravenous hippuric acid, 0.15 Gm.; prothrombin time was 35 to 48 per cent of normal, and cholesterol–cholesterol ester ratio, 164:28. Other values were: serum albumin, 2 Gm.; serum globulin, 4.3 Gm., and alkaline phosphatase, 12.5 Bodansky units per hundred cubic centimeters. The urinalysis, blood count, serodiagnosis and determinations of red cell fragility, nonprotein nitrogen, blood sugar and carbon dioxide–combining power were all unremarkable. The jaundice increased progressively. The patient began to show sensitivity to insulin. Increased breath sounds and

6. Laird, S. M.: Syringe-Transmitted Hepatitis, Glasgow M. J. **28**:199, 1947.

7. Droller, H.: An Outbreak of Hepatitis in a Diabetic Clinic, Brit. M. J. **1**:623, 1945. Hartfall, S. J.: Jaundice in Rheumatoid Arthritis, Lancet **2**:358, 1944.

8. Capps, R. B.; Sborov, V., and Schiefley, C. S.: A Syringe-Transmitted Epidemic of Infectious Hepatitis with Observations Regarding Incidence and Nature of Infectious Donors, J. A. M. A. **136**:819 (March 20) 1948.

rhonchi in the left side of the chest developed, and shortly thereafter the patient went from a lethargic state into coma and died February 17. Prior to death, the size of the liver had decreased noticeably on percussion. Autopsy revealed bronchopneumonia and acute yellow atrophy of the liver secondary to hepatitis.

HOMOLOGOUS SERUM HEPATITIS

In the present series, the mortality rate in homologous serum hepatitis was notably high: Seven of 17 cases (41 per cent) terminated fatally, indicating an unusually active type of virus. Serious consideration should be given the therapeutic use of blood or blood derivatives, such as plasma, convalescent serum and biologicals to which serum has been added. Undoubtedly, blood banks try to eliminate infectious persons from their lists of donors, but the possibility of the existence of subclinical forms of hepatitis or of recent hepatitis without jaundice cannot be overlooked. It is hoped that ultraviolet irradiation of blood and blood products will, in the future, eliminate this source of infection.

The following case report illustrates a fulminating and fatal type of homologous serum hepatitis due to a virulent icterogenic virus apparently introduced in blood plasma.

CASE 3.—E. D. P., a white veteran and truck driver of 21, entered the hospital Feb. 2, 1947 with a history of an infection of the upper respiratory tract followed by severe malaise, fatigue, progressive nausea and vomiting, pain in the right upper quadrant of the abdomen and dark urine of one week's duration. In December 1946 he had received 3 units of plasma during a transthoracic vagotomy for an intractable duodenal ulcer. The examination showed him to be acutely ill and icteric with tenderness in the right upper quadrant of the abdomen and a slightly enlarged liver. Laboratory values showed a range as follows: serum bilirubin, 15.7 to 19 mg. per hundred cubic centimeters; cephalin-cholesterol flocculation, 4 plus; prothrombin time, 4 to 7 per cent of normal; serum albumin, 4 Gm.; globulin, 2.3 Gm.; alkaline phosphatase, 20.4 Bodansky units, and blood urea nitrogen, 7 mg. per hundred cubic centimeters. A few tyrosine crystals were noted in a urinalysis on February 5. A complete blood count and examination of the spinal fluid were noncontributory. The sedimentation rate was normal, and blood cultures were sterile. The patient's course was rapidly downhill and was characterized by fever, lethargy, delirium, coma and death within five days after admission. An autopsy showed the cause of death to be acute yellow atrophy of the liver secondary to homologous serum hepatitis.

CHRONIC HEPATITIS

There is ample evidence provided by reliable investigators that chronic hepatitis and other sequelae may result from an acute attack of hepatitis. The incidence of chronic hepatitis is said to be low,[9] but acute hepatitis is stated to progress to the chronic phase in from 5 to

9. (*a*) Lucké, B.: Pathology of Fatal Epidemic Hepatitis, Am. J. Path. **20**:471, 1944; The Structure of the Liver After Recovery from Epidemic Hepatitis, ibid. **20**:595, 1944. (*b*) Young, L. E.: Current Concepts of Jaundice with Particular Reference to Hepatitis, New England J. Med. **237**:225, 1947.

50 per cent of cases.[10] According to Capps and his co-workers,[8] a prompt reaction to the direct test for bilirubinemia almost always indicates an active phase of the chronic form of the disease; Neefe [11] stated that this was also the first positive sign of early acute hepatitis. Although a fine distinction between chronic active and inactive hepatitis was not attempted in this series, the criteria established by Capps, his co-workers and other authors [12] were observed for the most part. Twenty-six patients in our series had chronic hepatitis. A history of acute hepatitis, with or without jaundice, within six months to five years of the onset of illness was obtained in each case. In addition to the bilirubinemia, in most cases fairly characteristic symptoms and hepatomegaly were present and responses to one or more hepatic tests were abnormal.

The following case is one of chronic and recurrent hepatitis of five years' duration; the condition showed some promise of improving.

CASE 4.—L. J. M., a white veteran and student of 27, was admitted Jan. 1, 1947 with incapacitating anorexia, weakness, malaise and loss of weight. He gave a past history of "catarrhal" jaundice in 1943 in New Mexico, with subsequent recurrent episodes, in Italy, in 1944 and 1945. A physical examination revealed mild, generalized icterus, a tender, firm, enlarged liver and a palpable spleen. Results of the laboratory tests ranged as follows: two hour urinary urobilinogen, 0 to 1.2 Ehrlich units, and serum bilirubin, 0.1 to 3.2 mg. per hundred cubic centimeters; icterus index, 6 to 21; thymol turbidity, 4.6 to 6.4 units; cephalin-cholesterol flocculation, 0 to 1 plus, and intravenous hippuric acid, 0.3 to 1.4 Gm. The sulfobromophthalein test showed 4 to 18 per cent dye retention, and the prothrombin time was 78 to 100 per cent of normal; the value for alkaline phosphatase was 4.2 to 4.5 Bodansky units per hundred cubic centimeters. Repeated investigations for blood dyscrasia and for the presence of malarial and intestinal

10. (*a*) Capps, Sborov and Barker.[8] (*b*) Barker, M. H.; Capps, R. B., and Allen, F. W.: Acute Infectious Hepatitis in the Mediterranean Theatre Including Hepatitis Without Jaundice, J. A. M. A. **128**:997, 1945. (*c*) Volwiler, W., and Elliot, J. A., Jr.: Late Manifestations of Epidemic Infectious Hepatitis, Gastroenterology **10**:349, 1948. (*d*) Klatskin, G., and Rappaport, E. M.: Late Residuals in Presumably Cured Acute Infectious Hepatitis, Ann. Int. Med. **26**: 13, 1947. (*e*) Bank, J., and Cheskin, L. J.: Hepatitis as Observed in Army General Hospital, Gastroenterology **6**:357, 1946. (*f*) Jersild, M.: Infectious Hepatitis with Subacute Atrophy of the Liver, New England J. Med. **237**:8, 1947.

11. Neefe, J. R.: Results of Hepatic Tests in Chronic Hepatitis Without Jaundice: Correlation with Clinical Course and Liver Biopsy Findings, Gastroenterology **7**:1, 1946.

12. (*a*) Capps, Sborov and Barker.[8] (*b*) Neefe.[11] (*c*) Capps, R. B.: The Present Status of Viral Hepatitis with Particular Reference to Chronic and Residual Forms, United States Veterans Administration Technical Bulletin 10-32, Washington, D. C., Government Printing Office, May 31, 1947. (*d*) Atschule, M. D., and Billigan, D. R.: Chronic Latent Hepatitis Following Catarrhal Jaundice, New England J. Med. **231**:315, 1944. (*e*) Kunkel, G.; Labby, D. H., and Hoagland, C. L.: Chronic Liver Disease Following Infectious Hepatitis: I. Abnormal Convalescence from Initial Attack, Ann. Int. Med. **27**:202, 1947.

parasites were noncontributory. Complete blood counts, and results of serologic studies and urinalyses, biopsy of a lymph node, determinations of the sedimentation rate and roentgenographic studies of the chest, gallbladder and gastrointestinal tract were normal. The patient was discharged as improved on August 9, only to present himself again in June and December of 1948 with symptoms of soreness in the right upper quadrant of the abdomen, easy fatigability, headaches and constipation. On each occasion, hyperbilirubinemia, hepatomegaly and splenomegaly were present. On the last admission, responses to all liver function tests returned to within normal limits prior to the patient's discharge from the hospital.

CHRONIC HEPATITIS

The clinical pattern of chronic hepatitis is uniformly similar to that of the acute form except for the variance in degree of the symptoms and signs, which have been well described in the literature. It may be well, however, to point out the striking symptoms and characteristic findings. Most commonly, a history of easy fatigability, mental depression and soreness, aching, fulness, heaviness or pain in the right upper quadrant of the abdomen is elicited. The last complaint is particularly noticeable after exercise or exertion. Other commoner symptoms are fat intolerance, flatulence, postprandial nausea and, occasionally, mild diarrhea. Capps [12c] stated that the disability is often pronounced and out of proportion to the general appearance of the patients. Attempts to pursue occupations or to perform jobs that were easily accomplished before the acute episode lead to an extreme degree of fatigability. There is a tendency to relapse and remission. In a severe relapse with jaundice, the findings are usually the same as those in the acute phase. The liver is almost always palpably enlarged and tender to a variable degree. Some pain may persist in the area of the liver after a sharp blow. There may be associated splenomegaly. Laboratory tests are apt to be misleading because of the paucity of abnormal responses, but usually bilirubinemia and one or more abnormal responses to liver function tests are observed, as listed in table 2.

The symptoms may simulate a psychoneurosis.[13] Ten per cent of our patients with chronic cases were admitted to the hospital with such a diagnosis. Since the diagnosis may be extremely difficult, in many cases the disease escapes recognition, according to Barker and others.[10b] Neefe [11] also found that the commonly used hepatic tests may fail to reveal hepatic disturbance in some cases in which the patients have incapacitating symptoms and for whom biopsy indicates chronic hepatitis. He stated that he considers the thymol turbidity, flocculation and colloidal gold tests the most sensitive indicators of this condition. Such was our conclusion in regard to the use of the thymol turbidity test in the present study.

13. (*a*) Bank and Cheskin.[10e] (*b*) Capps. [12c] (*c*) Sherlock, S., and Walshe, V.: Post-Hepatitis Syndrome, Lancet **2**:482, 1946.

It is now recognized that hepatitis may persist for a long time or relapse at intervals after an initial attack.[14] Hepatitis that persists beyond four to six months is considered to have reached the chronic phase.[15] Persistent or recurrent hepatitis lasting from four months to as long as twenty-nine years after the initial onset has been described by several investigators.[16] In the majority of these cases, biopsies of the liver indicated hepatitis, and the patients demonstrated the characteristic symptoms (hepatomegaly and impaired responses to liver function tests).

The majority of patients with acute infectious hepatitis for whom the disease is diagnosed early and properly managed to make a complete recovery. A small number die as a result of acute hepatic necrosis

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14. (*a*) Capps, Sborov and Barker.[3a] (*b*) Lucké.[9a] (*c*) Barker, Capps and Allen.[10b] (*d*) Volwiler and Elliot.[10c] (*e*) Klatskin and Rappaport.[10d] (*f*) Bank and Cheskin.[10e] Jersild.[10f] (*g*) Neefe.[11] (*h*) Capps.[12c] (*i*) Altschule and Billigan.[12d] (*j*) Kunkel, Labby and Hoagland.[12e] (*k*) Sherlock and Walshe.[12c] (*l*) Bloomfield, A. L.: The Natural History of Chronic Hepatitis (Cirrhosis of Liver), Am. J. M. Sc. **195**:429, 1938. (*m*) Krarup, N. B., and Roholm, K.: The Development of Cirrhosis After Acute Hepatitis Elucidated by Aspiration Biopsy, Acta med. Scandinav. **108**:306, 1941. (*n*) Turner, R. H.; Snavely, J. R.; Grossman, E. B.; Buchanan, R. N., and Foster, S. C.: Some Clinical Studies of Acute Hepatitis Occurring in Soldiers After Inoculation with Yellow Fever Vaccine, with Special Consideration of Severe Attacks, Ann. Int. Med. **20**:193, 1944. (*o*) Soffer, L. J., and Paulson, M.: Residual Hepatic Damage in Catarrhal Jaundice as Determined by Bilirubin Excretion Test, Arch. Int. Med. **53**:809, 1934. (*p*) Benjamin, J. E., and Hoyt, R. C.: Disability Following Postvaccinal (Yellow Fever) Hepatitis: Study of Two Hundred Patients Manifesting Delayed Convalescence, J. A. M. A. **128**:319 (June 2) 1945. (*q*) Brick, I. B.: Critique on Sequelae of Viral Hepatitis, Am. J. Digest. Dis. **15**:364, 1948. (*r*) Caravati, C. M.: Post-Hepatitis Syndrome, South. M. J. **37**:251, 1944. (*s*) Howard, R., and Watson, C. J.: Antecedent Jaundice in Cirrhosis of the Liver, Arch. Int. Med. **80**:1 (July) 1947. (*t*) Spellberg, M. A.: Sequelae of Acute Hepatitis, Am. Pract. **2**:311, 1948. (*u*) Kalk, H.: Chronic Forms of Epidemic Hepatitis with Regard to Their Clinical Symptomatology, Deutsche med. Wchnschr. **72**:471, 1947. (*v*) Marion, D. F.: Delayed Convalescence Following Acute Hepatitis: Clinical and Laboratory Evaluation, Gastroenterology **8**:717, 1947. (*w*) Flood, C. A., and James, E. M.: Clinical and Pathological Findings in Prolonged Hepatitis, ibid. **8**:175, 1947. (*x*) Mallory, F. B.: Cirrhosis of Liver: Five Different Types of Lesions from Which It May Arise, Bull. Johns Hopkins Hosp. **22**:69, 1911. (*y*) Kornberg, A.: Latent Liver Disease in Persons Recovered from Catarrhal Jaundice and in Otherwise Normal Medical Students as Revealed by the Bilirubin Excretion Test, J. Clin. Investigation **21**:299, 1944. (*z*) Polack, E.: Chronic Hepatitis in Young Persons With or Without Intermittent Jaundice, Acta med. Scandinav. **93**:614, 1938. (*a'*) Snell, A. M.: Fundamentals in the Diagnosis of Jaundice, J. A. M. A. **138**:274 (Sept. 25) 1948.

15. Barker, Capps and Allen.[10b] Neefe.[11] Capps.[12c]

16. Volwiler and Elliot.[10c] Klatskin and Rappaport.[10d] Altschule and Billigan.[12d] Flood and James.[14w]

or acute yellow atrophy. This pathologic change represents the extreme lesion of viral hepatitis. It is characterized by severe destruction of liver cells and an inflammatory reaction. There is no alteration of the framework of the liver. Scarring is not present. Hyperplasia of liver cells leads to the formation of new tissues producing coarsely nodular or tumor-like lesions. Healing gives rise to the so-called toxic cirrhosis, postnecrotic cirrhosis or coarsely nodular cirrhosis described by various authors.[17] According to Patek,[18] this form of cirrhosis also may eventually terminate in fatal hepatic insufficiency.

PORTAL CIRRHOSIS

The relation of hepatitis to cirrhosis of the liver is still a controversial subject. It is the opinion of some investigators [19] that hepatitis does not lead to cirrhosis of the liver. On the other hand, there is ample conclusive evidence, based on serial biopsies of the liver and on clinical observations and presented by other authors,[20] that hepatic cirrhosis

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17. Klatskin and Rappaport.[10d] Spellberg.[14t] Mallory.[14x] Bergstrand, H.: Ueber die akute gelbe Leberatrophie, mit besonderer Berücksichtigung ihres Auftretens in Schweden im Jahre 1927, Acta med. Scandinav., 1930, supp. 34, p. 331; Acta path. et microbiol. Scandinav., 1930, supp. 5, p. 41.

18. Patek, A. J., Jr.: Coarsely Nodular Cirrhosis, in Cecil, R. L.; McDermott, W., and Wolff, H. G.: A Textbook of Medicine, Philadelphia, W. B. Saunders Company, 1947, p. 867.

19. (*a*) Lucké.[9a] (*b*) Klatskin and Rappaport.[10d] (*c*) Dible, J. H.; McMichael, J., and Sherlock, S. V. P.: Pathology of Acute Hepatitis: Aspiration Biopsy Studies of Epidemic Arsenotherapy and Serum Jaundice, Lancet **2**:402, 1943. (*d*) Roholm, K., and Iverson, P.: Changes in Liver in Acute Epidemic Hepatitis (Catarrhal Jaundice) Based on Thirty-Eight Aspiration Biopsies, Acta path. et microbiol. Scandinav. **16**:427, 1939. (*e*) Karsner, H.: Morphology and Pathogenesis of Hepatic Cirrhosis, Am. J. Path. **13**:569, 1943. (*f*) Kalk, H., and Büchner, F.: Bioptic Picture of Epidemic Hepatitis (Laparoscopic and Microscopic Observations), Klin. Wchnschr. **24-25**:874, 1947.

20. Volwiler and Elliot.[10c] Bloomfield.[14l] Krarup and Roholm.[14m] Turner and others.[14n] Howard and Watson.[14s] Spellberg.[14t] Kalk.[14u] Marion.[14v] Polack.[14z] Snell.[14a'] Dible, McMichael and Sherlock.[19c] Roholm and Iverson.[19d] Jones, C. M., and Minot, G. R.: Infectious (Catarrhal) Jaundice: An Attempt to Establish a Clinical Entity, Boston M. & S. J. **189**:531, 1923. Sherlock, A.: Post-Hepatitis Syndrome, Lancet **1**:817, 1948. Wang, E.: Cirrhosis of Liver and Its Relation to Acute Epidemic Hepatitis, Nord. med. **32**:2634, 1946. Findlay, G. M.; Martin, N. H., and Mitchell, J. B.: Hepatitis After Yellow Fever Inoculation: Relation to Infective Hepatitis, Lancet **2**:301, 1944. Rennie, B., and Pirie, T. G.: Infective Hepatitis with Special Reference to Prognosis, Am. J. M. Sc. **210**:18, 1945. Axenfeld, H., and Brass, K.: Klinische und bioptische Untersuchungen über sogennanten Icterus catarrhalis, Frankfurt. Ztschr. f. Path. **57**:147, 1942. Eppinger, H.: Die Leberkrankheiten; Allgemeine und spezielle Pathologie und Therapie der Leber, Vienna, Julius Springer, 1937.

(Footnote continued on next page)

may be a sequela of hepatitis. It is certainly reasonable to assume that acute, chronic or recurrent hepatitis will produce hepatic damage, regeneration and fibrosis compatible with portal cirrhosis. The end result has been described in diverse fashion and under many titles. Pathologically it may be difficult to distinguish the various types; yet, clinically the important pictures are common to all at some time during the course of the disease. The relationship of clinical hepatitis to cirrhosis was substantiated by biopsies of the liver or by autopsy in 3 cases.

The following report of a case illustrates a transition of acute infectious hepatitis to portal cirrhosis.

CASE 5.—L. L. T., a white veteran and farmer of 57, entered the hospital May 14, 1948 with postprandial pain in the right upper quadrant of the abdomen, nausea, vomiting, clay-colored stools, dark urine and jaundice. He also had a past history of a chronic, recurrent duodenal ulcer. Examination showed jaundice, hepatomegaly and tenderness in the right upper quadrant. The results of laboratory studies were as follows: serum bilirubin, 0.5 to 10.8 mg. per hundred cubic centimeters; icterus index, 134 to 152; two hour urine urobilinogen, 0 to 5.9 Ehrlich units per hundred cubic centimeters; thymol turbidity, 2.3 to 18 units; cephalin-cholesterol flocculation, 2 to 4 plus, and prothrombin time, 43 to 100 per cent of normal. The sulfobromophthalein test showed 3 per cent dye retention and the intravenous hippuric acid test 0.4 to 0.6 Gm. The value for serum albumin was 2.2 Gm.; for serum globulin, 2.5 Gm., for alkaline phosphatase, 11.2 to 26 Bodansky units per hundred cubic centimeters. A series of fluoroscopic studies of the gastrointestinal tract revealed a duodenal ulcer. Initial blood counts, urinalyses, serologic studies and an electrocardiogram were normal. Determinations of the sedimentation rate and values for nonprotein nitrogen, blood sugar and amylase were noncontributory. A biopsy on June 8 showed pronounced disruption of the liver architecture. There were areas in which the tissue appeared necrotic, particularly in the vicinity of the portal triad. The cord cells varied considerably in size and staining property. Nuclei of many cells were enlarged and the cell cytoplasm swollen. The cells were deeply pigmented. Bile thrombi were not seen. There was some increase in connective tissue elements. Three weeks later, a second biopsy specimen revealed less polymorphonuclear cell activity, an increase of fine, fibrous tissue and infiltrations by fibroblasts within the portal areas. These findings were consistent with early cirrhosis. At that point, the red blood cell count gradually dropped to 2,700,000 per cubic millimeter and the hemoglobin concentration to 10.5 Gm. per hundred cubic centimeters. The patient gradually improved, both from the clinical standpoint and from that of laboratory tests, although hepatomegaly persisted. He was discharged on September 29. Three months later, he remained asymptomatic and no enlargement of the liver was noted. However, the response to the cephalin-cholesterol flocculation test was 2 plus, and that to the intravenous hippuric acid test, impaired.

Lichtman, S. S.: Hepatic Insufficiency, Ann. Int. Med. **25**:456, 1946. Watson, C. J., and Hoffbauer, F. W.: Problem of Prolonged Hepatitis with Particular Reference to Cholangiolitic Type and to Development of Cholangiolitic Cirrhosis of Liver, ibid. **25**:195, 1946. Snell, A. M.: Some Clinical and Physiologic Problems in Cases of Portal Cirrhosis, North Carolina M. J. **8**:338, 1947.

The following case illustrates the transition of chronic infectious hepatitis of four years' duration into portal cirrhosis.

CASE 6.—F. J. L., a white veteran of 31, was admitted Feb. 14, 1947. On entry, he complained of weakness, nausea, vomiting, anorexia, intolerance to fats and jaundice. He gave a past history of having had hepatitis with jaundice (in North Africa) in 1943, with a recurrence in 1947. Examination showed generalized icterus with an enlarged, firm, tender liver. Laboratory studies demonstrated the following values: serum bilirubin, 0.4 to 3.8 mg. per hundred cubic centimeters; icterus index, 9 to 26, and two hour urinary urobilinogen, 0.3 to 1.74 Ehrlich units per hundred cubic centimeters. The value for the thymol turbidity test was 3.9 to 19.6 units, and that for the cephalin-cholesterol flocculation test, 0 to 3 plus; the sulfobromophthalein test showed 0 to 20 per cent dye retention and the intravenous hippuric acid test 0.61 to 0.9 Gm. The prothrombin time was 60 to 100 per cent of normal. The serum protein values were: albumin, 3.9 to 5.4 Gm., and globulin, 2.7 to 1.8 Gm. per hundred cubic centimeters; the value for alkaline phosphatase was 3.7 to 12.1 Bodansky units per hundred cubic centimeters. The sedimentation rate ranged from 42 to 66 mm. (Westergren method) in one hour. The blood counts, urinalyses and serologic tests were not remarkable. A biopsy done on February 25 showed the liver architecture to be fairly well preserved. The individual cord cells were hyperplastic and showed a slight increase in vacuolization. Within the portal areas, there was a slight to moderate increase of fibrous tissue accompanied with fibroblasts and slight hyperplasia of the bile ducts. Scattered lymphocytes were present in the portal areas. Some liver cells were stained with bile. Thrombi were not particularly evident. Four weeks later, another biopsy disclosed findings compatible with portal cirrhosis. The patient was discharged on April 11 and was seen again in September and in February 1948, at which times his condition was consistent with that of compensated portal cirrhosis.

Another 100 patients with portal cirrhosis, whose cases are not reported here, were encountered during the study. Many gave a past history of jaundice. Because there was no conclusive evidence obtained to show that hepatitis was the initial hepatic disorder in these cases, the patients were not included in the series.

STUDIES OF LIVER FUNCTION

The laboratory tests most used in the series are listed in table 2. Some idea of the degree of usefulness of an individual test may be obtained by noting the percentage of cases in which the procedure was confirmatory of the clinical diagnosis. For example, elevation of the value for serum bilirubin was noted in 83.8 per cent of 93 cases. Nine of the 15 patients that had a normal value for serum bilirubin showed an elevated icterus index at some time during the course of illness. This illustrates the importance of repeating the tests. In our experience, the thymol turbidity test of Maclagan was more sensitive than that for cephalin-cholesterol flocculation, the response to the former being abnormal in 90 per cent of cases as against 75 per cent for the latter. This experience is not in accordance with the findings of

Mateer and his associates,[21] who, in an evaluation of this very point, found the cephalin-cholesterol flocculation test of Hanger to be the more sensitive and the better screening test. However, critical evaluation would depend on whether one were using the tests in acute or chronic hepatitis. The response to the thymol turbidity test is said to be more frequently abnormal in acute hepatitis, while the value for cephalin flocculation is oftener positive in chronic hepatitis and cirrhosis. Our statistics show that in 31 cases of acute hepatitis in which values for cephalin-cholesterol flocculation and thymol turbidity were both

TABLE 2.—*Analysis of Pertinent Physical Findings and Laboratory Tests*

	Normal Range	Number of Cases	Cases in Which Response Was Abnormal	
			Number	Percentage
Serum bilirubin, mg. per 100 cc.— 1 min.	0-0.2	..	..	....
25 min.	0.2-1.0	98	78	83.8
Jaundice	.....	100	72	72.0
Hepatomegaly	.....	100	57	57.0
Splenomegaly	.....	100	12	12.0
Cephalin-cholesterol flocculation (48 hr.)	0-1 plus	88	66	75.0
Thymol turbidity, units (30 min.)	0-4	60	54	90.0
Urinary urobilinogen, Ehrlich units per 100 cc. (2 hr.)	0-1.0	70	51	72.8
Prothrombin time, per cent of normal	70-100	74	39	52.7
Sulfobromophthalein retention, per cent (5 mg. per Kg. body weight; 45 min.)	0-5	42	32	76.0
Hippuric acid synthesis, Gm. (intravenous)	0.7-1.0	67	38	56.7
Alkaline phosphatase, Bodansky units per 100 cc.	2-6	35	23	65.7
Serum protein, Gm. per 100 cc.				
Total	6-8.3	..	..	....
Albumin	3.8-6.1	..	..	....
Globulin	1.2-3.0	57	28	49.0
Serum cholesterol				
Total, mg. per 100 cc.	140-250	..	..	....
Esters, per cent	40-60%	14	11	78.5

determined, the former was abnormal 27 times and the latter 26 times. In such tests in 21 chronic cases, the value for cephalin-cholesterol flocculation was abnormal 10 times and that for thymol turbidity 18 times. The value for thymol turbidity remained significantly abnormal longer than the responses to any of the other liver function tests used in the study.

The prothrombin time was below normal in 52.7 per cent of 74 cases. In the majority of these cases, there was no significant rise in the prothrombin time within twenty-four to forty-eight hours after the parenteral administartion of vitamin K. It is of interest to note that

21. Mateer, J. G.; Baltz, J. I.; Comanduras, P. D.; Steele, H. H., and Brower, S. W.: Further Advances in Liver Function Tests, and the Value of a Therapeutic Test in Facilitating the Earlier Diagnosis and Treatment of Liver Impairment, Gastroenterology **8**:52, 1947.

the lowest recorded prothrombin time in the 10 cases of fatal hepatitis varied from 4 to 36 per cent of normal. Of the nonfatal cases, in only 6 was the time below 43 per cent of normal and the lowest was 33 per cent of normal. The over-all average lowest prothrombin time in the nonfatal cases was 60 per cent of normal. In our experience with hepatitis, a prothrombin level below 40 per cent of normal was of serious prognostic import.

The sulfobromophthalein test demonstrated retention of the dye in 76 per cent of 42 cases. Mateer and his co-workers [21] classed this as one of the best of the screening tests, but it is believed to be of limited value in the presence of jaundice. Elevation of the quantity of blood phosphatase occurred in 65.7 per cent of 35 cases. Only 3 patients had elevations slightly above 20 Bodansky units per hundred cubic centimeters.

We used the test for hippuric acid synthesis (intravenous technic) in 62 cases. Patients in 56.7 per cent of this group showed impairment of this function. Values for urinary urobilinogen were abnormal in 72.8 per cent of 70 cases, the accuracy comparing favorably with that of any other liver function tests. In the determination of total cholesterol and of cholesterol esters, the ester fraction was found to be below normal in 11 of 14 cases. These tests may be of considerable value in differentiating intrahepatic and extrahepatic jaundice. We believe that had serial liver function tests been performed in all cases the percentage of abnormal tests would have been considerably higher.

MORTALITY

In general, the mortality rate in infectious hepatitis is reportedly low,[1] whereas that in homologous serum hepatitis is variable. In the epidemic of 1942, the mortality rate in 51,337 cases was 0.24 per cent.[22] In the epidemic of 1943 to 1945, the mortality rate in 68,000 cases was 0.3 per cent, according to Lucké and Mallory.[23] Neefe [11] listed the mortality rate as ranging from 0.2 to 0.5 per cent. Contrariwise, in Jersild's [10f] series of 550 patients the condition became chronic in 154 and of these 67 per cent died of subacute yellow atrophy. The majority of those who succumbed were in the older age group. Wood and Black [24] also reported a high mortality rate from serum

22. Walker, D. W.: Some Epidemiological Aspects of Infectious Hepatitis in the United States Army, Am. J. Trop. Med. **25**:75, 1945.

23. Lucké, B., and Mallory, T.: The Fulminant Form of Epidemic Hepatitis, Am. J. Path. **27**:867, 1946.

24. Wood, D. A., and Black, M. B.: Further Notes on Pathology of Acute Epidemic Hepatitis and Homologous Serum Jaundice, Am. J. Clin. Path. **16**:746, 1946.

hepatitis, particularly among wounded men. In our series, as shown in table 1, 2 of 45 patients with acute infectious hepatitis succumbed; the mortality rate was 4.4 per cent. The cause of death for 1 patient, a white man of 63, was extensive hepatic necrosis; it was revealed by autopsy. The second case was that of a white girl of 13, who presented a clinical picture of severe acute infectious hepatitis five months before death. Necropsy showed subacute hepatitis, lobular hepatic regeneration and early portal cirrhosis. Eight of 24 patients with inoculation hepatitis died, the mortality rate being 33 per cent. The mortality rate for the entire series was 10 per cent. There were no fatalities among the patients with chronic hepatitis or hepatitis of infectious mononucleosis or brucellosis during the two and one-half year period of observation.

TREATMENT

In general, the treatment outlined by Capps [12c] was followed. It consisted of adequate rest, nutritious diet and avoidance of hepatotoxic agents. Our patients were maintained on complete bed rest until the value for serum bilirubin fell to within 1.0 mg. per hundred cubic centimeters or until the jaundice cleared. With the disappearance of tenderness of the liver and the return to normal of the responses to liver function tests, the patient was permitted graduated activities. If there was no return of symptoms or change in liver function, the patient was considered to have made a complete recovery. Otherwise, complete bed rest was reinstituted.

The diet consisted of 450 Gm. of carbohydrate, 150 Gm. of protein and 100 Gm. of fat. Until the full diet was tolerated, the parenteral administration of a 10 per cent dilution of dextrose in isotonic sodium chloride solution with soluble vitamins was considered helpful.

Methionine, given in doses of 1 to 2 Gm. three times daily, appeared to have some beneficial effect in chronic hepatitis. Alcoholic beverages were interdicted. Surgical procedures were not only deferred in the acute phase but considered to be contraindicated, and intercurrent or focal infections were treated cautiously.

SUMMARY

One hundred patients with hepatitis were observed over a period of two and one-half years. The series included cases of acute infectious hepatitis, chronic or recurrent hepatitis, homologous serum hepatitis, syringe-transmitted or needle-transmitted hepatitis and hepatitis caused by other diseases. Six representative cases are described.

The virus of homologous serum hepatitis and of needle-transmitted or syringe-transmitted hepatitis may be extremely virulent. Effective measures to combat this mode of transmission are mentioned.

The apparent transition from hepatitis to portal cirrhosis was observed in 3 cases, as manifested by the clinical course of the disease, by biopsy of the liver or by necropsy. Of the 100 patients studied, 26 had chronic or recurrent forms of hepatitis.

The significance of liver function tests is discussed. In our experience, the tests for thymol turbidity, cephalin-cholesterol flocculation and cholesterol–cholesterol ester ratio were the most sensitive in acute hepatitis. A prothrombin time below 40 per cent of normal in acute hepatitis usually signified a poor prognosis. The sulfobromophthalein and thymol turbidity tests were the best indicators of chronic hepatitis.

Treatment of hepatitis is outlined.

Dr. W. A. D. Anderson, Professor of Pathology and Bacteriology, Marquette University School of Medicine; Dr. Joseph M. Lubitz, Pathologist, Veterans Administration Hospital, and Dr. Joseph F. Kuzma, Pathologist, Milwaukee County Hospital, made the pathologic studies in this paper.

DEFECT OF THE VENTRICULAR SEPTUM

Summary of Twelve Cases and Review of the Literature

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UNCOMPLICATED defects in the interventricular septum are among the earliest of the congenital cardiac malformations to be recognized clinically. Henri Roger presented a remarkably accurate clinical description of this syndrome in 1879,[1] and the name *maladie de Roger* is frequently used in connection with defects of the ventricular septum. Roger's presentation was in the form of a clinical lecture without the benefit of illustration by an autopsy. In spite of an abundance of reports on single cases of defect of the ventricular septum, no series was collected until 1920, when Müller[2] reported 9 cases and gave a brief review of case reports collected from the literature; the paper was presented in a somewhat sketchy and unsystematic manner.

The basic information about the pathologic features and the clinical picture of defect of the ventricular septum was contained in Maude Abbott's monograph[3] and was based on her well known analysis of 1,000 autopsies in cases of congenital heart disease. She presented the isolated defect of the ventricular septum as a communication between the subaortic region of the left ventricle and the tricuspid area or, rarely, the conus arteriosus of the right ventricle. The defect is located in the basal part of the septum just in front of the membranous portion. Rarely, according to Abbott, defects are located in the lower, muscular part of the septum. She stated that the cardiac function is seldom interfered with, that symptoms are usually absent and that there is little change in the relative size of the ventricles and none in that of the two great arterial trunks. In contrast to all these negative factors, however, extremely loud systolic murmurs are present, the intensity

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1. Roger, H.: Recherches cliniques sur la communication congénitale des deux coeurs par inocclusion du septum interventriculaire, Bull. Acad. de méd. **8**:1074, 1879.

2. Müller, H.: Zur Klinik und pathologischen Anatomie des unkomplizierten, offenen Septum ventriculorum, Deutsches Arch. f. klin. Med. **133**:316, 1920.

3. Abbott, M. E.: Congenital Heart Disease, in Nelson Loose-Leaf Medicine, New York, Thos. Nelson & Sons, 1932, vol. 4, pp. 207-321.

of which Abbott stated varies inversely with the size of the defect. This clinical and pathologic picture of defect of the ventricular septum is essentially the one presented in most textbooks of cardiology and cardiovascular roentgenology.[4]

The presentation of the subject of defect of the ventricular septum in Taussig's recent monograph[5] differed considerably from the conventional view, just summarized. She divided defects of the ventricular septum into "simple" defect (*maladie de Roger*) representing congenital perforation of the ventricular wall and "high" defect caused by the failure of the aortic septum to meet the ventricular septum. According to Taussig's concept, blood is shunted in the first type from the left to the right ventricle, whereas in the second type blood flows through the defect almost directly to the pulmonary artery. In the latter case, large quantities of blood may be forced into the pulmonary artery, causing its enormous dilatation. This concept of "high ventricular septal defect" as distinct from the simple defect was, however, not documented with case reports or supported with references.

Recent studies on congenital heart disease by venous catheterization of the heart have shown that considerable quantities of blood can be shunted through the defect from the left to the right ventricle.[6] In some cases in which diagnosis was made by this method, there was considerable cardiac enlargement, which speaks strongly against the innocence of the defect as it was hitherto conceived.

The purpose of this report is to reinvestigate the subject by reviewing all available reports in the literature on cases in which autopsy was performed, also additional case reports from the files of the Department of Pathology of the Stanford University School of Medicine.

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4. White, P. D.: Heart Disease, ed. 3, New York, The Macmillan Company, 1944. Levine, S. A.: Clinical Heart Disease, ed. 3, Philadelphia, W. B. Saunders Company, 1945. Roesler, H.: Clinical Roentgenology of the Cardiovascular System, ed. 2, Springfield, Ill., Charles C Thomas, Publisher, 1943.

5. Taussig, H. B.: Congenital Malformations of the Heart, New York, Commonwealth Fund, 1947.

6. Handelsman, J. C.; Bing, R. J.; Campbell, J. A., and Griswold, H. E.: Physiological Studies in Congenital Heart Disease: V. The Circulation in Patients with Isolated Septal Defects, Bull. Johns Hopkins Hosp. **82**:615, 1948. Dexter, L.; Haynes, F. W.; Burwell, C. S.; Eppinger, E. C.; Sosman, M. C., and Evans, J. M.: Studies of Congenital Heart Disease: III. Venous Catheterization as a Diagnostic Aid in Patent Ductus Arteriosus, Tetralogy of Fallot, Ventricular Septal Defect and Auricular Septal Defect, J. Clin. Investigation **26**:561, 1947. Baldwin, E. D.; Moore, L. V., and Noble, R. P.: The Demonstration of Ventricular Septal Defect by Means of Right Heart Catheterization, Am. Heart J. **32**:152, 1946.

MATERIAL

The autopsy material of the department of pathology represented 7,243 autopsies performed during the period from July 1, 1932 to Dec. 31, 1947. Twelve cases of uncomplicated defect of the ventricular septum were noted and are briefly summarized.

In addition, 80 reports of cases of defect of the ventricular septum in which autopsy had been performed were collected from the literature. Maude Abbott (1931) included in a table data on 55 cases, of which 52 were reviewed.[7] This material was supplemented with more recent reports and a few additional older ones.[8]

It was thought to be of value in the presentation of some clinical features to compare defect of the ventricular septum with complete absence of the ventricular septum. For that purpose, 10 cases of trilocular heart with a single ventricle in patients who survived beyond infancy are also reviewed.[9]

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7. Bauer, D. de F., and Astbury, E. C.: Congenital Cardiac Disease: Bibliography of the One Thousand Cases Analyzed in Maude Abbott's Atlas, with Index, [References 215-240, 242-249, 251-255 and 257-260], Am. Heart J. **27**:688, 1944.

8. (*a*) Gallavardin, L.: Maladie de Roger avec cyanose par communication interventriculaire et phthisie fibreuse, Lyon. méd. **118**:1004, 1912. (*b*) Laubry, C.; Routier, D., and Soulié, P.: Les souffles de la maladie de Roger, Rev. de méd., Paris **50**:439, 1933. (*c*) Audibert, V.; Raybaud, A.; Giraud-Costa; Audier, and Mattéi: Endocardite maligne lente d'un orifice de communication interventriculaire, Ann. d'anat. path. **9**:563, 1932. (*d*) Pallase: Maladie de Roger suivie pendant vingt ans, Lyon méd. **155**:38, 1935. (*e*) Leech, C. B.: Congenital Heart Disease: Clinical Analysis of Seventy-Five Cases from the Johns Hopkins Hospital, J. Pediat. **7**:802, 1935. (*f*) Mason, D. G., and Hunter, W. C.: Localized Congenital Defects of the Cardiac Interventricular Septum: A Study of Three Cases, Am. J. Path. **13**:835, 1937. (*g*) Müller, H.: Ein Fall von unkompliziertem offenem Septum ventriculorum cordis (maladie de Roger) mit grosser Lücke, Schweiz. med. Wchnschr. **18**:289, 1937. (*h*) Seiler, S.: Ueber einen Fall von Vitium Cordis Congenitum (Ventrikelseptumdefekt Pulmonalinsuffizienz), Helvet. med. acta **6**:357, 1939. (*i*) Congenital Anomaly of Heart: Patent Interventricular Septum, Cabot Case 25321, New England J. Med. **221**:239, 1939. (*j*) Ash, R.; Wolman, I. J., and Bromer, R. S.: Diagnosis of Congenital Cardiac Defects in Infancy: A Study of Thirty-Two Cases with Necropsies, Am. J. Dis. Child. **58**:8 (July) 1939. (*k*) Hanna, R.: Cerebral Abscess and Paradoxic Embolism Associated with Congenital Heart Disease: Report of Seven Cases, with a Review of the Literature, ibid. **62**:555 (Sept.) 1941. (*l*) Tucker, A. W., and Kinney, T. D.: Interventricular Septal Defect (Roger's Disease) Occurring in a Mother and Her Six-Month Fetus, Am. Heart J. **30**:55, 1945. (*m*) Welsh, K. J., and Kinney, T. D.: The Effect of Patent Ductus Arteriosus and of Interauricular and Interventricular Septal Defect on the Development of Pulmonary Vascular Lesions, Am. J. Path. **24**:729, 1948.

9. (*a*) von Rokitansky, C.: Die Defecte der Scheidewände des Herzens, Vienna, W. Braumüller, 1875. (*b*) Mann, J. D.: Cor Triloculare Biatriatum, Brit. M. J. **1**:615, 1907. (*c*) Marchand, F.: Eine seltene Missbildung des Herzens eines Erwachsenen (Tranposition der grossen Arterien bei rudimentärem rechten

The autopsy protocols and clinical charts were carefully reviewed. The important pathologic data included the size and weight of the heart; the size, shape and position of the septal defect; the size and position of the great vessels and their branches; the thickness of the wall of the two ventricles, and the presence of associated anomalies. The clinical data included physical findings; results of roentgenologic and electrocardiographic examination; the presence or absence of cyanosis, polycythemia and clubbing; the course; complications, and the cause of death.

Data on these factors were also assembled, whenever available, from case reports collected from the literature.

In order to extract useful information from the largest possible number of cases reported in the literature, those incompletely reported were included if the reports contained adequate information about any of the three factors: (*a*) size and position of the defect, (*b*) size of the cardiac chambers and the great arterial trunks and (*c*) clinical data.

All cases in which there were important malformations of the heart other than the septal defect were eliminated. However, minor congenital abnormalities were present in some cases included in this series, such as deformities or an abnormal number of the valve cusps, small patency of the foramen ovale or incomplete obliteration of the ductus arteriosus (the last two in infants), if it was thought that these associated changes had not essentially altered the cardiodynamics.

In some cases of the older group, defects of the ventricular septum were associated with acquired cardiac disease (aortic valvular disease, hypertension, etc.). Such cases were included with certain limitations: Such measurements and changes as could have been altered by the presence of secondary lesions were excluded from the tabulations.

SUMMARY OF CASES

CASE 1.—M. C., a 7 year old boy, was hospitalized because of septicemia following acute otitis media. A congenital anomaly of the heart had been diagnosed at the age of 4. Roentgenographic examination at the age of 6 had revealed the heart shadow to be at the upper normal limit. During the terminal illness, physical

Ventrikel), Verhandl. d. deutsch. path. Gesellsch. **12**:174, 1908. (*d*) Steinwider, C. D., and McPeak, E. M.: Congenital Absence of the Interventricular Septum in an Adult Laborer: Case Report, Texas State J. Med. **25**:341, 1929. (*e*) Favorite, G. O.: Cor Biatriatum Triloculare with Rudimentary Right Ventricle, Hypoplasia of Transposed Aorta and Patent Ductus Arteriosus, Terminating by Rupture of Dilated Pulmonary Artery, Am. J. M. Sc. **187**:663, 1934. (*f*) Peters, M.: Cor triloculare biatriatum mit Endocarditis lenta pulmonalis, Centralbl. f. allg. Path. u. path. Anat. **62**:52, 1935. (*g*) Trilocular Heart, Cabot Case 28532, New England J. Med. **227**:1045, 1942. (*h*) Glendy, M. M.: Glendy, R. E., and White, P. D.: Cor Biatriatum Triloculare: Case Report, Am. Heart J. **28**:395, 1944. (*i*) Vann, H. M., and Miller, R. E.: A Case of Pseudo-Monoventricular Heart Terminating in Brain Abscess, Anat. Rec. **88**:155, 1944.

examination revealed slight cardiac enlargement, a systolic thrill in the third intercostal space at the left sternal border and a harsh systolic murmur, loudest at the same area but well heard over the entire precordium. No other abnormalities of the cardiovascular system were noted. A blood culture was positive for hemolytic streptococcus. The boy had a septic type of temperature and died in coma ten days after admission.

Autopsy revealed acute otitis media, mastoiditis with thrombosis of the jugular vein and acute nephritis. The heart appeared normal, and measurements of the four orifices and of the thickness of the ventricular walls were within normal limits for the age of the child. The ventricular septum was perforated with a small tract which when dilated measured 3 mm. in diameter. It was located just underneath the posterior aortic cusp and led to the region of the tricuspid valve in the right ventricle. Other findings were of little importance.

Case 2.—E. O., a girl of 14, was hospitalized because of fever and weight loss of six weeks' duration. She was known to have had heart disease since the age of 3 years and at the age of 6 was kept in bed for six months because of a "leaky valve." Examination of the patient in the hospital revealed slight cardiac enlargement. There was a systolic thrill and a loud, harsh systolic murmur at the left sternal border, loudest at the fourth costal cartilage. An early diastolic blowing murmur was heard at the same area. The blood pressure was 130 systolic and 30 diastolic, and there was a collapsing quality of the pulse.

The electrocardiogram showed a normal P-R interval, with QRS complexes measuring 0.07 seconds; tall diphasic QRS complexes (R_1, 8 millivolts; R_2, 13 millivolts; S_2, 8 millivolts; R_3, 13 millivolts, and S_3, 12 millivolts) were noted in leads II and III. Roentgen examination was reported as revealing cardiac enlargement involving all chambers, but predominantly the left ventricle. The aortic shadow was small. There was no dilatation of the shadow of the pulmonary artery, but the hilar shadows were prominent.

The patient ran a febrile course. Blood cultures were positive for Streptococcus viridans. She died suddenly two weeks after admission.

Essential autopsy findings were a fatal subdural hemorrhage and septicemia due to Streptococcus viridans. The heart was a little larger than normal; the thickness of the cardiac muscle of the two ventricles was within normal limits. The tricuspid orifice was of normal circumference, but the valve consisted of only two cusps. Underneath the medial attachment of the cusps, there was a fistula measuring 4 mm. in diameter, which entered the left ventricle just underneath the right aortic cusp. Soft, friable vegetations were present around the fistula. The pulmonary, mitral and aortic orifices showed normal measurements. The pulmonary artery was normal. There was a slight deformity of the posterior aortic cusp, which was adherent to the right cusp. A large mass of vegetations was present on the right aortic cusp overlying the septal defect, and a smaller mass, at the posterior cusp. An aneurysm measuring 11 mm. in diameter was found in the anterior leaflet of the mitral valve, which was about 4 mm. deep and was filled with vegetations. A small triangular opening was noted at the bottom of the aneurysm, measuring 1.5 mm. on each side.

Case 3.—A man of 64 was hospitalized because of dyspnea, anorexia, insomnia and weakness, which gradually developed over a period of several weeks. He had led an active life as a plumber and had spent many years in the Orient, where he had become addicted to opium. He was said to have contracted syphilis at 45, the treatment of which consisted of only a few injections.

Examination revealed an enlarged heart and a loud systolic and an early diastolic blowing murmur over the entire precordium (heard best along the left

sternal border). The blood pressure was 120 systolic and 40 diastolic. The patient's course was rapidly downhill; he lapsed into coma and died three days after admission.

Pertinent autopsy findings were as follows: the somewhat enlarged heart, weighing 480 Gm. showed dilatation and hypertrophy of both ventricles (the pulmonary, tricuspid and mitral orifices were not remarkable); the aortic valves were almost completely filled with fresh vegetations, apparently originating on the posterior aortic cusp. The other cusps were normal except for small calcified nodules. A defect of the ventricular septum 7 mm. in diameter was found underneath the aortic valves; it led to the area of the right ventricle underneath the tricuspid valve and was completely filled with fresh vegetations. The aortic ring was somewhat stiffened by a calcific process, measuring 7 cm. in diameter, but the aorta beyond it was almost completely free from atheroma. A microscopic section through the septal defect showed it to be undoubtedly congenital in origin.

CASE 4.—A woman of 66 was known to have had heart disease since the age of 7 months and had been dyspneic on exertion since the age of 12 years. At 15, she had been kept in bed for several months because of a febrile illness thought to be acute rheumatic fever. Afterward, she had suffered from repeated attacks of "heart trouble," necessitating occasional periods of staying in bed for a few weeks at a time. At the age of 63, frank cardiac decompensation developed, which was at first controlled by medical management, but for the last one and one half years of life the patient was a complete cardiac invalid. She was known to have arterial hypertension and atrial fibrillation for at least two years before death. Examination during the terminal hospitalization revealed blood pressures averaging 200 systolic and 100 diastolic and the usual signs of congestive cardiac failure. The heart was enlarged to the left, and there was a systolic thrill at the apex and a harsh systolic and a blowing early diastolic murmur over the entire precordium. The rhythm of the cardiac beat was completely irregular. There was slight clubbing of the fingers. Laboratory findings were within normal limits. Hemiplegia developed, and the patient died.

The autopsy, limited to the heart, showed a large organ weighing 550 Gm. There was hypertrophy of both ventricles, more prominently of the right one. The tricuspid ring was dilated, but the size of other orifices was within normal limits. Just underneath the posterior aortic cusps, there was a defect in the ventricular septum, measuring 4 mm. in diameter, which opened into the right ventricle in the region of the posterior leaflet of the tricuspid valve. The defect was lined with endocardium. Opposite its outlet into the right ventricle, on the anterior wall of the myocardium of the right ventricle and below the pulmonary valves, there was a patch of thickening of the endocardium measuring 3.5 by 2.5 cm.

CASE 5.—A baby girl was born at term and was noted to have harelip. Heart sounds at the age of 1 day were not remarkable. At the age of 2 weeks she was noted to become cyanotic during feeding and was found to have a loud systolic murmur and thrill over the precordium; afterward, she had frequent "cyanotic spells." A roentgenogram of the chest taken at 4 weeks showed cardiac enlargement. On the twenty-eighth day, the child became more cyanotic, the temperature rose to 39.6 C. (103.3 F.), the respiration became rapid and she died.

At autopsy, the heart weighed 75 Gm. (twice normal). The foramen ovale was patent and measured 0.5 cm. in diameter. A large defect in the ventricular septum, measuring 1 cm. in diameter, connected the region of the left ventricle below the aortic valves with the tricuspid region of the right ventricle. The pulmonary artery and the aorta both measured 2 cm. in diameter. The two ventricles were equal in thickness of the wall, measuring 4 mm. There was a small ductus arteriosus measuring 2 mm. in diameter.

CASE 6.—A male infant was born at term and was well for three days; hematuria, melena and, finally, spasticity of both legs then developed. A systolic murmur over the precordium was noted on the fourth day. The baby died at the age of 7 days with signs of widespread hemorrhage.

At autopsy, hemorrhages were found in the lungs, kidneys and intestines. The heart weighed 30 Gm. The ductus arteriosus was patent but not more than 2 mm. in diameter. The foramen ovale was patent but protected by the usual valve. Measurements of the orifices were as follows: pulmonary, 2 cm; aortic, 2 cm.; tricuspid, 4 cm., and mitral, 3 cm. The walls of the ventricles measured 7 mm. on the left and 3 mm. on the right. A defect in the ventricular septum was located in the muscular portion, connecting the apical, lower portion of the left ventricle with the region of the posterior papillary muscle in the right ventricle. It was lined with smooth epithelium and measured 4 mm. in diameter.

CASE 7.—A man of 53 was hospitalized repeatedly during the last three years of life because of classic signs and symptoms of cirrhosis of the liver, associated with mild diabetes. At no time were there any symptoms referable to the cardiovascular system. On examination, the heart was usually reported as normal except for an apical systolic murmur. One observer reported a harsh systolic murmur heard over the entire precordium, about a year before the patient's death. During the terminal admission, after a severe gastrointestinal hemorrhage, a physical examination of the heart was reported as noncontributory. Slight clubbing of the fingers was noted. The patient died suddenly.

Autopsy revealed Laennec's cirrhosis of the liver with multiple esophageal varices, one of which ruptured, causing a fatal hemorrhage. The heart appeared normal on inspection and weighed 360 Gm. The foramen ovale admitted a probe but was protected by the usual flap. All the orifices and valves were normal. On the ventricular septum, 1 cm. underneath the posterior aortic cusp, there were two cup-shaped depressions, one of which contained a hole 3 mm. in diameter leading to the right ventricle, just underneath the tricuspid valve. The great vessels were normal.

CASE 8.—A premature female infant was delivered at 8 months, weighing 2 pounds 13 ounces; she died thirteen hours after birth.

Autopsy showed cerebral hemorrhage. The heart was about normal in size. The valves, orifices and myocardium appeared normal. There was a defect in the muscular part of the ventricular septum, measuring 0.5 by 1 cm. The foramen ovale was open in only a small area.

CASE 9.—A female fetus, stillborn at term, was found at autopsy to have multiple congenital defects: harelip, cleft palate, bilateral clubbed feet and Meckel's diverticulum. The heart weighed 12 Gm. and appeared dilated. A 1 cm. defect in the membranous portion of the ventricular septum connected the region of the left ventricle just underneath the aortic ring with the outlet of the right ventricle, being almost covered with a leaflet of the tricuspid valve. The muscular wall of both ventricles measured 2 mm.; the valves were normal.

CASE 10.—An apparently normal female infant died three days after birth with signs suggestive of pneumonia.

Autopsy showed partial atelectasis of the lungs. The heart weighed 20 Gm. There was a defect in the membranous part of the ventricular septum, measuring 0.8 cm. in diameter. The foramen ovale was patent and had the normal flap. The cardiac valves and orifices were normal. The ductus arteriosus was patent.

CASE 11.—A premature (7½ months) stillborn fetus was delivered by cesarean section, weighing 1,600 Gm.

The heart weighed 9 Gm. There was a 0.5 cm. triangular defect in the membranous septum. The ventricles and valves and the great vessels appeared normal. Both orifices of the coronary arteries were moved toward the commissures between the cusps rather than occupying a portion midway between the commissures.

CASE 12.—A male infant, born at term, was shown to have atresia of the esophagus and a bracheoesophageal fistula. He was operated on at the age of 4 days and died eight days later with signs of respiratory difficulty.

Autopsy showed massive aspiration bronchopneumonia. The heart seemed large for the infant's size. A small hole was found in the membranous portion of the ventricular septum; otherwise, the heart and the great vessels were normal.

SUMMARY OF AUTOPSY FINDINGS IN NINETY-TWO CASES OF DEFECT OF THE VENTRICULAR SEPTUM

The 80 reports of cases of defect of the ventricular septum collected from the literature and the 12 cases reported in this paper were analyzed and the important clinical and pathologic data tabulated.

Incidence.—It is exceedingly difficult to determine the frequency of congenital heart disease and the relative frequency of various malformations. The rarity of the condition makes statistics based on hospital material subject to considerable error, and, in addition, such factors as the interest of the hospital staff in the subject may influence the reliability of statistics. In order to estimate roughly the incidence of uncomplicated defect of the ventricular septum, the number of cases of this malformation was compared with the incidence of two other congenital malformations, defect of the atrial septum and tetralogy of Fallot. Table 1 presents the incidence of these three syndromes in our autopsy material as compared with other, similar series.[10] It may be seen that defect of the ventricular septum and defect of the atrial septum are roughly comparable in frequency and are commoner than tetralogy of Fallot. It seems that this compilation of data, in spite of some limitations, is more reliable than Abbott's analysis of 1,000 cases based entirely on case reports from the literature. In Abbott's series, cases of tetralogy of Fallot are most numerous, those of defect of the atrial septum next and those of defect of the ventricular septum rarest of the three types. This difference is best explained by the fact that rare malformations are more readily reported in the literature than the commoner ones.

10. (*a*) McGinn, S., and White, P. D.: Progress in the Recognition of Congenital Heart Disease, New England J. Med. **214**:763, 1936. (*b*) Philpott, N. W.: Relative Incidence of Congenital Cardiac Abnormalities in Montreal Hospitals, J. Tech. Methods **15**:96, 1937. (*c*) Ingham, D. W.: Congenital Heart Disease: Incidence at the Mayo Clinic, ibid. **18**:131, 1938. (*d*) Clawson, B. J.: Types of Congenital Heart Disease in 15,597 Autopsies, Journal-Lancet **64**:135, 1944. (*e*) Gibson, S., and Clifton, W. M.: Congenital Heart Disease: A Clinical and Postmortem Study of One Hundred and Five Cases, Am. J. Dis. Child. **55**:761 (April) 1938.

Age and Sex.—The age of patients in this series varied from that of a premature stillborn fetus to 79 years. The sex distribution was 46 males and 42 females; the sex was not mentioned in 4 cases. The ages at death were distributed as follows: less than 1 year, 26 cases; 1 to 5, 18; 6 to 10, 8; 11 to 15, 5; 16 to 20, 11; 21 to 30, 7; 31 to 40, 9; 41 to 50, 2; 51 to 60, 1; 61 to 70, 3, and over 70, 2.

TABLE 1.—*Incidence of Defect of the Ventricular Septum, Defect of the Atrial Septum and Tetralogy of Fallot*

Source	Number of Autopsies	Patients with Defect of the Ventricular Septum (Uncomplicated)	Patients with Defect of the Atrial Septum (Including Widely Open Foramen Ovale)	Patients with Tetralogy of Fallot
Present series	7,243	12	7	9
McGinn and White [10a]	7,500	5	9	3
Philpott [10b]	7,240	11	5	10
Ingham [10c]	8,314	2	21	1
Clawson [10d]	15,597	37	7	9
Gibson and Clifton [10e] (infants and children only)	1,960	12	23	8
Totals	47,844	80	72	40

Size of Defect.—Table 2 presents the size of the defect in 78 cases in which measurement of the interventricular foramen was reported. In this and the following tables, the data are presented in three age groups:

TABLE 2.—*Size of Defect of the Ventricular Septum in 78 Patients in Various Age Groups*

Size of Septal Defect	Patients			
	Under 1 Year	1 to 15 Years	Over 15 Years	Total
Actual diameter				
Less than 5 mm	6	10	9	25
5 to 10 mm	7	17	11	35
1 to 2 cm	4	2	7	13
Over 2 cm	1	1	3	5
Size in relation to cardiac size				
Small	1	5	9	15
Medium	4	18	11	33
Large	12	5	7	24
Extremely large	1	3	3	7

patients below the age of 1 year, those from 1 to 15 and adults (in the case of infants the value of clinical information is very limited). While division into still smaller age groups would appear desirable, it is impracticable because of the small number of cases.

The second part of table 2 represents an effort to estimate the size of the ventricular foramen in relation to the size of the heart in children. The size of the foramen was compared with the width of the aorta or

with the over-all measurement of the heart so as to make it roughly comparable to the classification adopted for fully grown hearts (0 to 5 mm. diameter, small defect; 6 to 10 mm., medium-sized defect; 11 to 20 mm., large defect, and over 20 mm., extremely large defect). This is an arbitrary classification suitable only for defects of the ventricular septum, as defects in the atrial septum are, on the average, considerably larger.

It is shown in the table that small and medium-sized defects are commoner than large ones, especially in the older group.

Location of Defect.—The important information as to the location of the defect in the ventricular septum was available in 65 cases. Defects were divided in three groups (table 3): those specifically

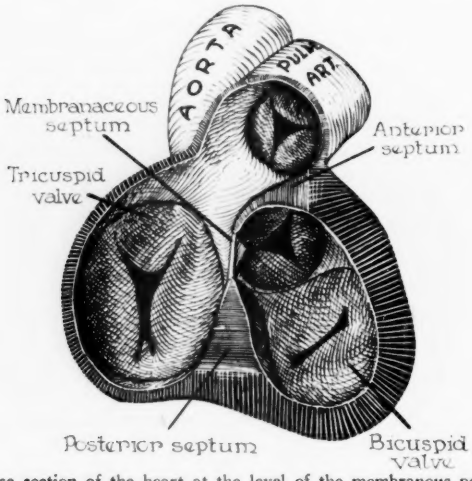
TABLE 3.—*Location of Defects of the Ventricular Septum in 65 Cases in Which Autopsy Was Performed*

Location of Defect	Patients			
	Under 1 Year	1 to 15 Years	Over 15 Years	Total
1. Underneath aortic valve (in left ventricle)				
a. Leading to tricuspid region of right ventricle	11	7	16	34
b. Leading to conus arteriosus	0	2	2	4
c. Location of opening to right ventricle unspecified	4	2	5	11
d. Membranous portion of septum (multiple perforations)	0	1	1	2
2. In upper portion of septum (no more exact location reported)	3	2	3	8
Total defects in basal portion of ventricular septum	18	14	27	59
3. In lower or muscular portion of ventricular septum	3	2	1	6

described as located just beneath the aorta valve (in the left ventricle), which were instances of the typical "interventricular foramen"; those described as "upper defects" without a more specific location, which are presumed to have been instances of typical interventricular foramen, and, finally, defects in the lower part of the septum, located at least 1 cm. below the insertion of the aortic valve. Subaortic defects were then divided into those in which the opening of the right ventricle was located close to the median leaflet of the tricuspid valve; those located more anteriorly, leading to the conus arteriosus, and those in which the location of the aperture of the right ventricle was not specified. In addition, there were 2 cases in which multiple perforations of the membranous portion of the septum were reported. Category 1 *a* in table 3 represents the typical interventricular foramen (Keith),[11] which

11. Keith, A.: The Hunterian Lectures on Malformations of the Heart, Lancet **2**:359, 433 and 519, 1909.

involves the posterior part of the anterior portion of the septum (figure) and the front part of the membranous portion of the septum. In most cases a small part of the membranous portion of the septum was still identifiable; in some it was entirely absent, and in such cases the lesion was often reported as a "defect in the undefended space." Type 1 *b* is a defect in the anterior portion of the septum, with the membranous portion of the septum intact and, usually, with muscular tissue dividing it from the defect. Both these types (1 *a* and 1 *b*) are identical with ventricular defects associated with complex malformations of the heart, notably, pulmonary stenosis and transposition of the arterial trunks.



Transverse section of the heart at the level of the membranous portion of the septum, looking up toward the great vessels (adapted from von Rokitansky [9a]).

Table 3 shows that defects in the lower septum were rare, constituting less than 10 per cent of the series.

Effect on Pulmonary Circulation.—Pathologic changes usually associated with prolonged overloading of the pulmonary circulation include hypertrophy of the right ventricle, dilatation of the pulmonary artery and its branches and pulmonary arteriosclerosis. Only the first two of these three factors were considered in this series, because too few observations were made in pulmonary arteriosclerosis. The classification of hypertrophy of the right ventricle was arbitrary; in adults, the condition of the wall of the right ventricle was classified as normal if it measured less than 5 mm. in thickness; if the wall measured 5 to 7 mm. the condition was listed as hypertrophy and the condition of a still thicker wall was classified as severe hypertrophy. In addition,

the impression of the pathologist and—in the absence of hypertrophy of the left ventricle—the ratio of the thickness of the wall of the left ventricle to that of the wall of the right ventricle were considered in estimating the degree of hypertrophy of the right ventricle, especially in children.

TABLE 4.—*Relation Between Size of Defects of the Ventricular Septum and Degree of Hypertrophy of the Right Ventricle**

Size of Defect	Condition of Right Ventricle		
	Normal	Slight Hypertrophy	Severe Hypertrophy
Small	XXXX OOO	XX O	....
Medium	..... OO	XX OOOO	X O
Large	..... OOO	XX OOO	XXX OOOO
Extremely large	....	X	XXX O

* "X" represents a patient over 15 years of age; "O," one 15 or under.

Because of the physiologic preponderance of the defects of the right side of the heart and of the pulmonary circulation on that side in the fetus and in early life, the observations of the effect of defects of the ventricular septum on the pulmonary circulation were limited to patients

TABLE 5.—*Relation Between Size of Defects of the Ventricular Septum and That of the Pulmonary Artery**

Size of Defect	Size of Pulmonary Artery	
	Normal	Dilated
Small	XX	XXX
Medium	.... OO	X OO
Large	.... O	XXXXXX OOOOO
Extremely large	X	X O

* "X" represents a patient over 15 years of age; "O," one 15 or under.

over 1 year old. Table 4 presents the relationship between the size of the defect of the ventricular septum and the degree of hypertrophy of the right ventricle in the 41 cases in which data were available on both factors. It is shown that hypertrophy of the right ventricle is commonly associated with defect of the ventricular septum and that a rough relationship exists between its degree and the size of the defect.

Table 5 shows a relationship between the size of the septal defect and dilatation of the pulmonary artery in 25 cases.

Physical Signs.—The classic sign of ventricular septal defect is the Roger murmur, a loud, long, rough systolic murmur in the third and fourth intercostal space at the left sternal border, associated with a systolic thrill in that area. In this series, reports on physical examinations were accepted in 70 cases; in the remainder they were not available or were rejected because of associated lesions. Table 6 shows the incidence and location of the murmurs in the various age groups and indicates also whether the defects were large, medium or small. The absence of any murmur was reported in 5 cases, involving 2 infants and 3 adults. In 1 case only, a diastolic murmur but no systolic murmur was reported. In all other cases, systolic murmurs were noted, mostly in the classic location but occasionally higher up, in the pulmonary area, or lower, at the apex. No evidence of a change in physical signs was seen with age except in the increasing number of early diastolic blowing murmurs at the left sternal border associated with systolic murmurs. Characteristic systolic murmurs were reported as early as a few days after birth. In 4 cases the systolic murmurs were described as "soft"; in most others they were loud or extremely loud. It is fully realized that data on subjective physical findings, such as cardiac auscultation, collected from many authors writing in different periods, are of limited value; nevertheless, one gathers the impression that there is no relationship between the size of the defect and the presence and intensity of the murmur, as was claimed by some, nor could the location of the murmur be definitely related to the size or anatomic position of the defect.

TABLE 6.—*Incidence of Murmurs of Defect of the Ventricular Septum in Relation to Size of the Defect and Age of the Patient*

	Patients											
	Under 1 Year				1 to 15 Years				Over 15 Years			
Murmurs	S*	M	L	T	S	M	L	T	S	M	L	T
Systolic (at left sternal border)												
At second interspace	0	0	0	0	0	3	1	4	2	1	0	3
At third or fourth interspace	2	4	0	6	7	5	0	12	2	8	6	16
"Apical"	0	1	0	1	0	1	2	3	2	0	1	3
"Precordial"	0	4	1	5	2	2	0	4	1	6	1	8
Diastolic												
With systolic				0				2				8
Alone				0				0				1
None	0	2	0	2	0	0	0	0	0	2	1	3

* S indicates a small defect; M, a medium-sized one; L, a large one, and T, the total defects in each group.

Cyanosis.—As expected, cyanosis was absent from most cases in this series; yet, some cases reported were characterized by chronic cyanosis not associated with cardiac failure, and these deserve a careful analysis. In 2 cases [12] described as instances of uncomplicated defect of the ventricular septum, the aorta was reported as overriding the defect, and the cases were eliminated from the series as representing examples of the Eisenmenger complex. In 3 others, chronic cyanosis was reported:

Müller's case [8g] was that of a man of 26 in whom mild to moderate cyanosis with clubbing and polycythemia had gradually developed between the ages of 20 and 23. At the age of 26 cardiac failure developed, and the patient died. He was found to have a severely hypertrophied right ventricle and a dilated pulmonary artery. A "typical" subaortic defect of the ventricular septum, measuring 1.5 cm. in diameter, was found, the upper edge of which was formed by the aortic valve.

Seiler [8h] reported the case of a woman of 22 who died of a cerebral abscess. The patient had had dyspnea and cyanosis since childhood, was somewhat underdeveloped and, at the age of 19, had been found to have the triad of moderate cyanosis, clubbing and polycythemia. In addition, there was roentgenologic and electrocardiographic evidence of severe overloading of the pulmonary circulation. The autopsy revealed prominent hypertrophy of the right side of the heart, with a dilated and sclerotic pulmonary artery and an oval defect 11 by 6 mm. in the membranous septum.

Tucker and Kinney [8i] reported a case of Roger's disease in a pregnant woman of 20. She had been found to be slightly cyanotic and dyspneic at the age of 4½. She was described as showing intermittent cyanosis, particularly after exercise or exposure to cold. During pregnancy frequent attacks of extreme dyspnea and intense cyanosis developed, and the patient was found to have moderate cyanosis, clubbing and questionable polycythemia; she died in cardiac failure. Autopsy revealed marked hypertrophy of the right ventricle, but no dilatation of the pulmonary artery. A defect 2 cm. in diameter was found in the typical location. A published photograph of the specimen showed the defect and the position of the aorta and suggested that the aorta may have been slightly overriding.

The summary shows that the clinical course in these 3 cases was similar to that in cases of the Eisenmenger complex. The relationship of uncomplicated defects of the ventricular septum to the Eisenmenger complex will be discussed in detail. In addition, 4 cases were reported in which there was questionable or intermittent cyanosis: There were 2 cases of children, aged 2¼ and 4½ years,[13] with septal defects mea-

12. Lindeboom, G. A.: Morbus Caeruleus in Patient with Open Ventricular Septum, Nederl. tijdschr. v. geneesk. **83**:5555, 1939. Tesseraux, H.: Zur Kentniss der Defekte des Herzkammerscheidewand, Virchows. Arch. f. path. Anat. **289**:412, 1933.

13. Dupre, E.: Communication congénitale des deux cœurs, par inocclusion du septum interventriculaire avec rétrécissement de partère pulmonaire chez un jeune homme de vingt-et-un ons, Bull. Soc. anat. de Paris **66**:404, 1891. Carpenter, G.: Specimen of Congenital Morbus Cordis, Rep. Soc. Stud. Dis. Child. **6**:241, 1906.

suring 5 and 6 mm., respectively; the third case was that of Laubry's youth of 18,[8b] who had a "typical" septal defect 1 cm. in diameter and complicating slight aortic incompetence. He was reported to have slight cyanosis but no clubbing or polycythemia. Gallavardin[8a] reported the case of a woman of 23 who died of pulmonary tuberculosis and who had had moderate cyanosis of unknown duration. She was found to have a large "typical" defect of the ventricular septum, a prominently dilated pulmonary artery, and severe hypertrophy of the right ventricle.

Roentgenographic and Electrocardiographic Findings.—Considering the small number of case reports in which these findings were made available, only a few remarks are possible. A total of 10 reports on roentgenograms were found. In 2 of them, the heart was reported as normal. In 6 cases, cardiac enlargement was noted without a more detailed description. In 2, cardiac enlargement was associated with prominent enlargement of the pulmonary artery and its branches, presenting the configuration which is usually thought to be characteristic of defect of the atrial septum or the Eisenmenger complex; in each case, a large defect of the ventricular septum was present.

In 10 cases, reports on electrocardiographic examinations were presented. Normal curves were reported in 2 cases and right axis deviation in 3. High voltage, diphasic QRS complexes, such as were described in our case 2, were noted in 4 cases. In 1 other case, there was a typical right bundle branch block. In 4 of these 5 cases with abnormal QRS complexes, large defects were noted.

Even with this fragmentary information, it appears probable that electrocardiographic changes and roentgenographic abnormalities are likely to appear prominently in the presence of large septal defects.

Defects in the Lower Portion of the Septum.—It was thought to be of importance to separate defect in the lower part of the ventricular septum, in view of Taussig's division of defect of the ventricular septum into "high" and simple types. Table 7 presents the pertinent data in the 6 cases of defects of the lower portion of the ventricular septum in this series and, in addition, in a seventh case, in which multiple perforations of the lower part of the septum were reported. The patients in 3 of these cases were newborn infants not suitable for clinical analysis. Of the remaining 4 cases, a small defect was present in 2 and a large defect in 1. In the last, hypertrophy of the right ventricle and dilatation of the pulmonary artery were reported. Murmurs were reported in 4 cases, and in 3 of them the location was given: One was reported in the typical location, 1 at the apex and 1 at the xiphoid process. It is impossible to judge from these cases whether or not an atypical location of the murmur is of diagnostic significance

for defects in the lower portion of the septum. It appears, however, that in all other respects these cases did not present any distinctive features and that except for the location they were clinically and pathologically similar to those of other defects of the ventricular septum.

Complete Absence of the Ventricular Septum.—The trilocular heart with a single ventricle is a rare malformation; an occasional survival beyond infancy has been noted. This lesion differs from simple defect of the ventricular septum only in degree and has been placed with it in a single group by one author [14]; yet, the complete absence of the septum and the fact that one of the great arterial trunks is usually hypoplastic alters the circulation to such a degree that only certain

TABLE 7.—*Summary of Findings in Cases of Defect of the Lower Portion of the Ventricular Septum*

Source	Age and Sex of Patient	Physical Signs	Cause of Death	Size of Defect	Condition of Right Ventricle	Condition of Pulmonary Artery
Duckworth [13a]	Newborn M	.....	Asphyxia	"Crow-quill"	.....	.....
Present series	7 days M	Systolic murmur	Hemorrhage	0.5 cm.	Normal	Normal
Present series	13 hours F	.....	Hemorrhage	0.5 by 1 cm.	.....	Normal
Müller [8g]	1 yr., 9 mo. M	Systolic murmur at third rib, left sternal border	Broncho-pneumonia	3 mm.	Dilated	Enlarged
Mason and Hunter [8f]	12 years M	.....	Unknown (sudden death)	1 by 0.8 cm.	Hyper-trophy	Dilated
Carey [13a]	37 years M	Systolic murmur at apex	Cirrhosis of liver	4 mm.	Normal	.....
Weiss [13a]	79 years M	Systolic murmur at xiphoid process	Uremia	Small (multiple)	Normal	Normal

clinical features can be compared in these two syndromes. Those which were thought to be useful for the analysis of the clinical features of defect of the ventricular septum were as follows: (*a*) the presence of systolic murmurs in the trilocular heart; (*b*) the presence or absence of cyanosis, and (*c*) the incidence of conduction defects in the electrocardiogram.

The patients in the 10 cases of trilocular heart died at the ages of 8 to 36 years. For 8 of the cases, a report on physical findings was

13a. Cited by Bauer and Astbury.[7]

14. Schnitker, M. A.: The Electrocardiogram in Congenital Cardiac Disease: A Study of One Hundred and Nine Cases, One Hundred and Six with Autopsy, Cambridge, Mass., Harvard University Press, 1940.

available, and in all these, loud systolic murmurs were present. The location was reported as "precordial" in 3, "apical" in 2 and "pulmonary" in 3. In 4 cases, diastolic murmurs were also heard.

Cyanosis was present in all cases except 1, in which it was questionable. In 7 cases, cyanosis was severe and had been present since childhood. In 2 cases, it appeared late and was mild.

Electrocardiograms were described in 4 cases. In all of them, tall, wide, diphasic QRS complexes were reported.

Associated Lesions.—Whereas major associated congenital malformations were eliminated by excluding cases of these disorders from the series of cases of defect of the ventricular septum, a number of defects were present which were thought to be of little importance from the standpoint of cardiodynamics. The distribution of these associated lesions was as follows: anatomic patency of the foramen ovale, 12 cases; incomplete obliteration of the ductus arteriosus (cases with widely patent ductus were eliminated), 4; bicuspid pulmonary valves, 2; bicuspid aortic valves, 3; retraction and deformity of the posterior aortic cusp, 3; deformity of the median tricuspid leaflet, 3, and right-sided aortic arch, 1.

Cases of acquired cardiac lesions included 4 of calcific aortic stenosis, the lesions in 3 of them being superimposed on bicuspid valves. In 2 cases, rheumatic endocarditis was diagnosed, involving the mitral valve in 1 and the mitral and tricuspid valves in the other. In none of these cases of acquired valvular lesions were the deformities severe. Bacterial endocarditis involved, in addition to the interventricular foramen, the pulmonary valve in 5 cases and the aortic valve in 4.

Prognosis.—The prognosis in congenital cardiac malformations was expressed by Abbott in terms of the average duration of life in her series of cases collected from the literature. It gave, however, a misleading impression, since the calculation was influenced by the large number of infants. It was thought that a much fairer view of the severity of the lesion could be presented by means of an analysis of the causes of death in a series of cases, with an effort being made to separate the cases in which the causes of death were directly related to the malformation from those in which the patient died from unrelated causes. Such an analysis is presented for the series of cases of defect of the ventricular septum in table 8, in which the incidence of death from the four commonest causes in congenital heart disease is contrasted with that from coincidental and unrelated causes. Cardiac failure was responsible for a moderately small number of deaths, whereas bacterial endocarditis appeared a more important hazard. Pulmonary tuberculosis and cerebral abscess were relatively unimportant. The majority of patients died of causes unrelated to the cardiac malformation, mostly noncardiac.

It is fully realized, however, that the presence of cardiac disease in these cases may have been a contributory factor in some of these unrelated deaths, the importance of which cannot be estimated.

Pursuing this line of reasoning further, it was noted that of the 6 adults who died of cardiac failure, the oldest was 66. Two patients had complicating hypertension. The duration of cardiac insufficiency

TABLE 8.—*Cause of Death in 85 Cases of Defect of the Ventricular Septum in Relation to Age Groups*

Cause of Death	Patients			Total	
	Under 1 Year	1 to 15 Years	Over 15 Years	Number	Percentage
Cardiac failure	1	6	6	13	15
Bacterial endocarditis	0	9	9	18	20
Tuberculosis of lungs	0	1	4	5	6
Cerebral abscess	0	1	2	3	4
Other causes	20	11	15	46	55

from onset to death varied from a few weeks to two years. One patient had atrial fibrillation.

COMMENT

Pathogenesis of Defect of the Ventricular Septum.—Defects in the ventricular septum have attracted less attention as isolated lesions than in combination with other malformations. Von Rokitansky[9a] presented in his classic monograph on defects of the cardiac septums 24 reports of cases of defect of the ventricular septum, but in all of them associated malformations were present. He concluded that other defects, notably pulmonary stenosis and the overriding aorta, are the primary cause and that the defect of the ventricular septum is the result of combined malformations. This view has been accepted with modifications ever since. The most important question in connection with the series of cases analyzed in this paper is whether the pathogenesis of uncomplicated defect of the ventricular septum is basically different from that of septal defects constituting a part of the tetralogy of Fallot or similar syndromes. This question has never been answered, nor has it been studied carefully. Keith,[11] states that cases of uncomplicated defect of the ventricular septum deserve further study, and Spitzer,[15] in his extensive monograph, made only a brief mention of simple defects.

15. Spitzer, A.: Ueber den Bauplan des normalen und missbildeten Herzens: Versuch einer phylogenetischen Theorie, Virchows Arch. f. path. Anat. **243**:81, 1923.

It is shown in this report that the great majority of uncomplicated defects of the ventricular septum are located immediately underneath the aortic valve. This location of the defect is identical with those constituting a part of complex cardiac malformations.

One of the most important contributions to the study of congenital heart disease is the work of Spitzer,[15] who studied the phylogenetic and ontogenetic mechanism of certain cardiac malformations and postulated a uniform mechanism of all defects associated with various types of transposition of the arterial trunks. He included in his concept of transposition the overriding of the aorta over a septal defect (Spitzer's type 1) and showed that within this type there is a considerable variation in the position of the aorta. In his series of cases of transposition, cases were included in which the aorta originated almost completely from the left ventricle (only one tenth of it was over the right ventricle). In such cases (no. 1 and 2 in Spitzer's report), the defect of the ventricular septum was for practical purposes "uncomplicated," since no associated malformations were present. Spitzer noted that smaller septal defects are usually associated with a lesser degree of overriding. He provided a common explanation for all malformations associated with any form of transposition in the theory of faulty torsion (detorsion) of the primitive cardiac tube.

Spitzer's theory has been generally accepted as the foundation of the modern knowledge of cardiovascular malformation, although some details of his theory have been criticized and modified.[16] It provides a basis for the unified classification of all subaortic defects of the ventricular septum regardless of associated lesions. It is possible that the process of maldevelopment (Spitzer's detorsion) causes in mildest cases small, uncomplicated defects of the ventricular septum, in more advanced cases defects combined with dextraposition of the aorta (Eisenmenger complex) with or without pulmonary stenosis (tetralogy of Fallot) and in most severe cases transposition of the arterial trunks (Spitzer's types 2, 3 and 4). This concept would place most cases of simple defect of the ventricular septum in the group of "transposition malformations," and it could perhaps be proved correct if other criteria of transposition than the position of the aorta (malposition of the coronary ostiums and of the bulbar ridges) were found in some of these

16. Pernkopf, E., and Wirtinger, W.: Die Transposition der Herzostien—ein Versuch der Erklärung dieser Erscheinung, Ztschr. f. Anat. u. Entwcklngsgesch. **100**:563, 1933. Harris, J. S., and Farber, S.: Transposition of the Great Cardiac Vessels, with Special Reference to the Phylogenetic Theory of Spitzer, Arch. Path. **28**:427 (Oct.) 1939. Lev, M., and Saphir, O.: A Theory of Transposition of the Arterial Trunks Based on the Phylogenetic and Ontogenetic Development of the Heart, ibid. **39**:172 (March) 1945. Saphir, O., and Lev. M.: The Tetralogy of Eisenmenger, Am. Heart J. **21**:31, 1941.

cases. To date, detailed studies of cases of uncomplicated ventricular septal defect are not available. One can, however, speculate by presenting arguments favoring such a concept: (*a*) It has been noted that a great majority of uncomplicated defects of the ventricular septum are identical in position and shape with those associated with, and caused by, dextraposition of the aorta; it appears unlikely that two different developmental errors would cause exactly the same morphologic changes. (*b*) The dividing line between simple defects of the ventricular septum and those combined with dextraposition (Eisenmenger complex) is indistinct.[17] Many patients reported as having Eisenmenger complex showed only minimal overriding of the aorta and could have been classified by some pathologists as having simple defects of the ventricular septum. Some patients reported as having defects of the ventricular septum, on the other hand, would have been better classified as having the Eisenmenger complex. There is obviously a transitional zone in which the pathologist finds it difficult to decide whether the position of the aorta justifies a classification of "overriding." The gradual transition between a septal defect with a normal position of the aorta and one with an unquestionable dextraposition suggests a common etiologic factor. (*c*) Even in the tetralogy of Fallot, which is the commonest and best known type of complex cardiac malformation, there are instances in which the aorta originates almost entirely from the left ventricle, and in which the morphologic appearance of the specimen indicates pulmonary stenosis combined with a simple ventricular septal defect. This also favors a common pathogenesis of all subaortic ventricular septal defects.

In considering the relationship between the Eisenmenger complex and simple defect of the ventricular septum, one should note the normal topographic relationship of the base of the aorta to the ventricular septum, as indicated in the illustration. The posterior portion of the anterior part of the septum and the anterior portion of the membranous part of the septum are located immediately underneath the aortic orifice. If these two parts of the septum are defective, the aorta comes in close contact with the right ventricle. Dextraposition and overriding could therefore be caused not only by an embryologic rotation of the aorta to the right but, perhaps, also by acquired changes developing in extrauterine life, such as deviation of the septum to the left or slight rotation of the aortic orifice on a posteroanterior axis.[17]

Defects other than subaortic ones originate by a different process of maldevelopment, probably an imperfect formation of the muscular portion of the septum. These defects are rare, and clinically they do not present a distinctive syndrome.

17. Selzer, A., and Laqueur, G.: The Eisenmenger Complex, to be published.

Effect of Defect of the Ventricular Septum on the Circulation.—Clinically, defect of the ventricular septum is usually pictured as a "functionally silent" lesion with little alteration of cardiodynamics.[18] This view would suggest that a fistulous connection between the two ventricles is of lesser importance than one between the atriums or between the arterial trunks, for both in defect of the atrial septum and in patent ductus arteriosus circulatory dynamics usually show considerable changes. It is evident from the results of the analysis of this series that such a view is incorrect. Pathologic findings in a large proportion of cases show changes indicative of considerable overloading of the pulmonary circulation. It has been shown that changes such as hypertrophy of the right ventricle and dilation of the pulmonary artery are related to the size of the defect and not to the position of it, as suggested by Taussig. In this connection, it is well to recall that acquired perforations of the ventricular septum, which occasionally occur in the course of acute myocardial infarction and are located in the muscular portion of the septum, are known to be associated with severe dilatation and failure of the right ventricle.

Whereas a defect of the ventricular septum, if large enough, may have a striking effect on the circulation, such large defects are less common than smaller ones. This preponderance of smaller defects which need not alter circulatory dynamics seems to be the reason for the older view that ventricular septal defect is an innocent cardiac malformation. The frequency of smaller defects is in line with the view expressed in the preceding paragraph, that large defects are caused by severer malrotation of the cardiac tube and, therefore, are more likely to occur in complex cardiac malformation than as isolated lesions.

Cyanosis.—In the presence of a normal relationship of pressure between the ventricles, oxygenated blood flows back into the right ventricle through the defect and cyanosis is absent; yet, chronic cyanosis associated with polycythemia and clubbing has been reported in some cases of allegedly uncomplicated ventricular septal defect. Since, at the time of writing, nobody has proved the existence of a deficiency in the oxygen exchange in the lungs in congenital cardiac malformation, it is believed that cyanosis is due to the admixture of venous blood in the arterial system. The reason for the entry of venous blood into the left ventricle is not clear. Whereas the pressure in the right ventricle may be considerably increased and true pulmonary hypertension may be present in patients with overloaded pulmonary circulation, it is doubtful whether pressure in the right ventricle

18. Laubry, C., and Pezzi, C.: Traité des maladies congénitales du cœur, Paris, J.-B. Ballière & fils, 1921.

could permanently exceed that in the left ventricle. In addition, every evidence points to the fact that the output of the right side of the heart considerably exceeds that of the left side, indicating a large over-all left to right blood shunt. One could postulate the presence of turbulence in the defect, allowing the free mixing of blood from both ventricles; this mechanism of cyanosis is the obvious one in hearts with a single ventricle. However, the size of the typical interventricular foramen makes the free mixing of blood in the presence of a large left to right fistula somewhat unlikely, for these defects seldom exceed 2 cm. in diameter and are considerably smaller than defects in the atrial septum. It should also be noted that cyanotic cases in this series were not necessarily those in which the largest defects occurred. The most likely factor facilitating the mixing of blood in the defect is the anatomic position of the aorta overriding the defect, in the presence of a large enough foramen and, perhaps, of high pressure in the right ventricle. The view has been expressed that in borderline cases overriding of the aorta could develop later in life and need not be due to congenital dextraposition. It is believed, then, that the presence or absence of cyanosis is the criterion distinguishing simple ventricular septal defect from the Eisenmenger complex, and one which may be more accurate than examination of the pathologic specimen. One can thus postulate that in cases of large ventricular septal defects located immediately underneath the aortic orifice, the presence of normal oxygen saturation of arterial blood justifies the classification of "uncomplicated ventricular septal defect" whereas the presence of arterial anoxemia calls for inclusion in the Eisenmenger group. This statement is based on the fact that morphologically there is no distinct dividing line between the two syndromes, and that the clinical, electrocardiographic and roentgenographic features of large ventricular septal defects and of the Eisenmenger complex are identical.

Little light is thrown on the question of *cyanose tardive*, or cyanosis due to the terminal reversal of the blood flow in the shunt. Such terminal cyanosis has been reported in a few cases, but it is exceedingly difficult to judge whether cyanosis appearing in the course of cardiac failure is more intense than that associated with failure without intracardiac shunt.

Clinical Features Other than Cyanosis.—Reports on physical examinations in cases of ventricular septal defect confirmed the frequency of loud, rough systolic murmurs best heard at the lower left sternal border. This Roger murmur occurred frequently enough to be considered pathognomonic for this syndrome. The often quoted statement that the intensity of such murmurs varies inversely with the size of the defect is not confirmed in this series, because the few instances

of soft murmurs or of absent murmurs were found not only with large defects but were scattered irregularly among the cases of various sizes of defects. In addition, the fact that loud systolic murmurs were present in all cases of complete absence of the ventricular septum speaks against the theory of inverse relationship between the size of the defect and the intensity of the murmur. The fact that in some cases murmurs were reported in other locations than that of the typical Roger murmur is not surprising, since commoner and better known murmurs, such as the one associated with aortic stenosis, also show frequent deviation from the "typical" location. In the rare cases in which mention was made of the transmission of murmurs, no regularity could be noted as to the direction of the transmission. Early diastolic blowing murmurs at the left sternal border were commonly noted, but it is not clear whether they originated in the defect or were due to relative pulmonary insufficiency. In cases in which large, pulsating pulmonary vessels are noted, the second possibility is more appealing.

Relatively few reports on roentgenographic examinations were available. Judging from those and from the appearance of the pathologic specimens, it seems logical to expect normal or insignificantly enlarged cardiac shadows in cases with smaller defects of the ventricular septum. In the presence of a large defect, the cardiac silhouette acquires the characteristic shape associated with overloading of the pulmonary circulation, such as occurs with large defects of the atrial septum or in the Eisenmenger complex, namely, enlargement of the heart with particular prominence of the conus arteriosus and the pulmonary artery and its branches, with pulsating hilar shadows and pulmonary congestion.

The electrocardiogram may be normal or may show preponderance of the right ventricle of various degrees, but apparently the most characteristic pattern for this syndrome is the presence of tall and diphasic QRS complexes in the conventional leads, with or without prolongation. This pattern is also noted in the case of the trilocular heart with a single ventricle; a relationship to the absence of a portion or all of the ventricular septum is therefore indicated. It should be noted, however, that intraventricular conduction defects occurring in congenital heart disease are not limited to lesions associated with defects in the ventricular septum: They were observed in cases of pulmonary stenosis with an intact ventricular septum.[19]

Prognosis.—The prognostic evaluation of a congenital malformation of the heart depends on two factors: the effect of structural abnormality on the circulation and the susceptibility to complicating infections. The first factor is the predictable one: Failure of the circu-

19. Selzer, A.; Carnes, W. H.; Noble, C. A.; Higgins, W. H., and Holmes, R. O.: The Syndrome of Pulmonary Stenosis with Patent Foramen Ovale, Am. J. Med. **6**:3, 1949.

lation occurs after years of stress and strain on the heart, which can be detected by the usual clinical methods, such as estimating the cardiac size, the size of the pulmonary vessels and the electrocardiographic evidence of ventricular strain. In the case of defect of the ventricular septum, patients showing evidence of a large interventricular fistula can be placed in the same category as those with large defects of the atrial septum and sizable ductus arteriosus: The lesions are not serious enough to interfere with growth and survival to adult life but reduce the life expectancy to a considerable degree, allowing only an occasional patient to survive beyond early middle age.

The hazard of bacterial infection applies in all cases, regardless of the size of the defect or of its effect on the circulatory dynamics. This susceptibility to subacute bacterial endocarditis is high: In this series, 28 per cent of the patients over 1 year of age died of this complication. The susceptibility to cerebral abscess is considerably less than that to bacterial endocarditis. The incidence of pulmonary tuberculosis was small in this series, and its occurrence was probably coincidental.

One is justified in concluding that the conventional concept of defect of the ventricular septum is not entirely correct, as it applies only to small defects. In these cases, moreover, the favorable prognosis is marred by a high susceptibility to bacterial endocarditis, the prevention of which should be the primary objective in the management of patients in this group.

With the increase in the size of ventricular septal defects, it becomes evident that the right side of the heart and the pulmonary circulation are profoundly affected by this malformation.

The diagnosis of congenital heart disease has been facilitated in recent years by the introduction of new methods, such as angiocardiography and venous catheterization of the heart. The first of these methods seems to be of little value in diagnosing a defect with a left to right intracardiac shunt. Venous catheterization of the heart, on the other hand, may demonstrate such a shunt if a highly oxygenated blood sample is obtained from the right ventricle. Proof of the infallibility of the newer method, however, will have to await correlation of the findings with the results of autopsy in a considerable series of cases.

SUMMARY AND CONCLUSIONS

Twelve cases of uncomplicated ventricular septal defect in which autopsy was performed are reported, and the clinical and pathologic findings in these and in 80 other cases in the literature are presented.

1. Taussig's division of defects of the ventricular septum into "simple" and "high" categories as clinical entities is not confirmed. In the vast majority of ventricular septal defects of all sizes there is a typical interventricular foramen, located in and anterior to the mem-

branous septum, connecting the area of the left ventricle immediately underneath the aortic valves with that of the right ventricle in front of the median leaflet of the tricuspid valve. Only in rare instances are defects of the lower portion of the septum located in the muscular part, and these present no distinctive clinical features.

2. It is suggested, in accordance with Spitzer's theory, that the typical interventricular foramen is related to the same process of maldevelopment which in severer forms causes the Eisenmenger complex, the tetralogy of Fallot and transposition of the arterial trunks. For that reason, the dividing line between the larger types of uncomplicated defect of the ventricular septum and the Eisenmenger complex is indistinct and all degrees of transitional forms can be found.

3. Cyanosis is absent from cases of uncomplicated defect of the ventricular septum. It is believed that any significant decrease in oxygen saturation in the arterial blood is due to congenital or acquired overriding of the aorta, and that cases in which this is found should be classified as instances of the Eisenmenger complex. It is suggested that the presence of cyanosis may be a more reliable factor in differentiating the two syndromes than the appearance of the pathologic specimen, since reconstruction of the aortic orifice in its proper relation to the defect during life may be difficult.

4. The effect of defect of the ventricular septum on the circulation is related to the size of the communication: Smaller defects may have no effect on circulatory dynamics, whereas larger ones almost always lead to considerable overloading of the pulmonary circulation with dilatation of the pulmonary artery and hypertrophy, strain and failure of the right ventricle.

5. The characteristic "Roger murmur," the rough and loud systolic murmur at the lower left sternal border, was observed fairly consistently in this series and can be considered pathognomonic for defect of the ventricular septum. Occasionally, however, systolic murmurs were located in other points of the chest wall or were soft or even absent. There was no apparent relation between the intensity of the murmur and the size of the defect, and loud systolic murmurs were heard in cases of complete absence of the ventricular septum. Early diastolic blowing murmurs at the left sternal border were common.

6. The roentgenologic appearance of the cardiac shadow varied from a normal cardiac silhouette to cardiac enlargement with prominence of the shadow of the pulmonary artery and that of its branches. In large defects, the configuration resembled that usually associated with defects of the atrial septum or the Eisenmenger complex.

7. Electrocardiographic findings also were variable, but in some cases intraventricular conduction defects with very tall diphasic QRS complexes were reported. These findings were also reported in cases with complete absence of the ventricular septum.

8. The prognosis in defect of the ventricular septum is favorable in milder cases and guarded in cases with large shunts. In all cases there is a relatively high susceptibility to bacterial infection of the endocardium, which accounted for 22 per cent of the deaths in this series.

PHYTOBEZOAR IN THE GASTRIC STUMP

Report of a Case and Discussion of Therapy

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ALTHOUGH there are 170 cases of phytobezoar to be found in the literature at the time of this report, the concretion apparently has never before been observed in the stump of a partially resected stomach.

REPORT OF CASE

An unmarried woman of 69 for many years had epigastric soreness after meals. During the past year deterioration, a 25 Kg. loss of weight, vomiting and occasional moderate episodes of diarrhea had occurred. For three months, the patient had usually been confined to bed. On admission to the surgical department (May 21) because of a suspected malignant growth in the antrum, the red blood cell count was 1,500,000 with 48 per cent hemoglobin and 2,100 leukocytes. The patient showed considerable weakness. The temperature rose to 38.5 C. (101.3 F). After four blood transfusions, the hemoglobin rose to 82 per cent with 3,700,000 erythrocytes, the temperature gradually subsided and high resection of the stomach was carried out (June 6). There was anacidity before as well as after the operation, and mucosal atrophy and chronic gastritis were noted in the resected specimen.

Soon after the operation, frequent vomiting developed, necessitating prolonged clinical treatment. No relation of the vomiting to meals was noted. Roentgenologically (July 18) the anastomosis was found to be very narrow, the gastric stump containing intermediary fluid. On August 4, the fluid had diminished somewhat. Five days later, however, a new roentgenoscopic examination was requested because of increased vomiting and epigastric pains. At that time (August 9), the stomach contained a coagulum 5 by 6 by 7.5 cm. (figure). Roentgen exploration on August 15 and 25 and on September 6 and 19 showed the coagulum to be gradually decreasing in size, and it was no more to be demonstrated on September 23. Retention of food particles, however, was observed on November 14. Because of the persistent vomiting and loss of weight, a new operation was performed on December 9. The anastomosis was found to be only 4 mm. in diameter. A new opening of 2 cm. was made.

REVIEW OF LITERATURE

The spontaneous disappearance of a phytobezoar (table 1) seems to be more frequent than would appear from the literature; in 9 recorded cases, it has been complete in 7. The longest estimated duration followed by complete disappearance has thus far been four weeks.

From the Roentgen Department (Head: O. Sandström, M.D.) and the Surgical Department (Head: H. Wahren, M.D.), Central Hospital.

I published a report of a case in which healing was spontaneous.[1] Later I observed 2 similar instances. In 1, a man of 50 even had a deep ulcer on the lesser curvature of the stomach; the foreign body disappeared in a week. In the other, in a middle-aged woman, it disappeared in some days. These observations indicate our lack of knowledge as to the number of spontaneous healings. The foreign bodies described in table 1 were composed of diverse vegetable materials; the percentage of persimmon balls was low in this series, although 70 per cent of all phytobezoars recorded in the literature have been composed of persimmons. A persimmon bezoar, once formed, seems to have special resistance.

Most phytobezoars have been removed surgically as soon as the diagnosis was established. Operation is indicated in long-standing

Phytobezoar in the gastric stump, showing progressive diminution in size *A*, three days; *B*, nine days, and *C*, nineteen days after onset of symptoms.

cases, especially in those in which persimmon balls or cellulose fibers, evidently resistant to digestion, made up the mass. On 17 occasions, however, the operation was performed during the first four weeks of the disease, that period being the longest time in which spontaneous disappearance has been noted (table 2); in 14 of these cases in which the outcome was stated it was favorable. Probably in some of them there would have been spontaneous disappearance. If a case is of less than four weeks' duration, it seems advisable to wait; apparently this has not been pointed out before. Provided the diagnosis has been secured and no complications demand immediate removal, the patient should be observed in the clinic. For the important differential diag-

1. Walk, L.: Gastroskopisch untersuchter Fall von Phytobezoar aus Beeren von Crataegus, Klin. Wchnschr. **19**:894-895, 1940.

TABLE 1.—*Summary of the Literature of Spontaneous Disappearance of Phytobezoar*

Author	Composition of Bezoar	Sex	Age	Duration of Bezoar before Hospitalization	Length of Hospitalization	Comment
Capelle (1861)	Vegetable debris containing calcareous substances	F	48	Epigastric tumor observed 4 weeks	Not hospitalized	Phytobezoar 9 cm. in circumference vomited after colocynth and mild mercurous chloride; disappearance of palpable tumor, and gradual subsidence of complaints; recovery (patient observed 5 years)
King (1894)	Persimmons	M	14	Unknown	2 weeks	Natural voiding after massage of tumor after 2 2 weeks' treatment
Hichens and Odgers (1912)	Coconut fibers	F	24	3 months	.....	Incomplete spontaneous passage (2 masses after 3 months; the rest later removed at operation)
Hart (1923) case 8	Prune and raisin skins	F	Middle-aged	Unknown	Some days	Achylia; spontaneous passage after administration of hydrochloric acid
DeBakey and Ochsner (1938-1939) case 6	Persimmons	M	37	Several months	14 days	Incomplete passage (another phytobezoar in stomach?)
Lawrie (1939)	Persimmons	M	28	9 days	22 days	Palpable mass rapidily diminished in size and finally disappeared after daily gastric lavage and massage
Walk (1941)	Hawthorne berries	F	57	4 weeks	Some days	Spontaneous passage after ulcer regimen, belladonna and magnesium oxide; complete recovery (patient observed 3 years)
Cambel and Konuralp (1943) case 1	Not stated	M	55	Unknown	Not stated	Phytobezoars (5.5 to 7.5 Gm.) vomited at gastric lavage by patients with stenosing cancer of the stomach
case 2	Not stated	M	46	Unknown	Not stated	

TABLE 2.—*Cases of Uncomplicated Phytobezoar, Operated on During the First Four Weeks of the Disease*

Author	Composition of Bezoar	Sex	Age	Duration of Bezoar Before Admission	Hospitalized Before Operation	Comment
Hart (1923) case 4	Persimmons	F	40	Some days	Not stated	Total duration of disease 7 days; no preoperative diagnosis
Hibi (1927) case 1	Persimmons	F	3	5 days	Not stated	Hospitalized for 22 days
Potter (1930)	Persimmons	M	57	3 weeks	6 days	Gastric ulcer
Castellani (1931)	Diospyros lotus	M	9	15 days	Some days	
Zaccaria (1931) case 3	Persimmons	..	8	20 days?	Not stated	Gastralgia during some months; loss of appetite; sometimes vomiting
Wyatt (1932)	Persimmons	F	52	4 days	Not stated	Three masses
Zanetti (1933)	Grape skins	..	14	8 days	Not stated	
Owen (1933) case 1	Persimmons	M	35	3 weeks	.....	
Henschen (1933)	Persimmons	F	6	2-3 weeks	Not stated	Palpable epigastric tumor; no roentgen examination
Murdock (1934) case 2	Persimmons	M	4	2 days	.....	Operated immediately. Two masses
Case 8	Persimmons	F	61	6 days	4 days	
Baur (1936)	Plant fibers (plums) and gummous substance	F	30	15 days	Not stated	Very small phytobezoar of the size of a filbert
Rutledge (1937)	Persimmons	M	24	10 days	3 days	Great prepyloric ulcer
White (1938) case 1	Persimmons	M	48	15 days	Not stated	2 similar attacks before onset of present illness (spontaneous passing of persimmon balls in some days?)
Woolsey (1938)	Persimmons	M	9	10 days	Not stated	
Gürkan (1943)	Not stated	F	50	25 days	Not stated	Slight gastric distress and loss of weight during some years
Peronato (1941) case 1	Diospyros lotus	F	8	20 days	1 day	Pasty, soft mass weighing 235 Gm.

nosis, gastroscopy has been valuable.[2] Repeated roentgenologic examinations, as in the present case, have apparently not been reported. The rapid diminution in size of a phytobezoar of short duration is probably important; by means of palpation even a persimmon bezoar has been observed to disappear spontaneously[3] (table 1). On the contrary, slight diminution in size in a case of long standing seems to lack prognostic value; it has been noted in 2 cases, in 1 roentgenoscopically and in the other by palpation. In the first of these,[4] two roentgenoscopic examinations were made with an interval of two months between them; operation had to be done. In the other,[5] an undiagnosed phytobezoar, although it diminished slightly to palpation, led to cachexia and, finally, to death.

The differentiation of phytobezoars formed of interlacing plant fibers from those composed of coagulated organic substance[6] has not been tested as to its clinical value. Dietetic treatment as for peptic ulcer, combined with the administration of antacid and antispasmodic drugs, has been used during hospitalization[1]; in the presence of achylia, hydrochloric acid has been administered.[7] In most cases of phytobezoar in which the gastric juice has been examined, free acid has been demonstrated and high acidity has been frequent. Anacidity has been observed in 4 cases only.[8] In my case, there was anacidity, and histologically mucosal atrophy and gastritis were observed. Gastric ulcer, frequent in phytobezoar, was not to be demonstrated. The usual

2. (*a*) Walk.[1] (*b*) Moersch, H. J., and Walters, W.: Phytobezoar with Visualization by Means of Gastroscopy, Am. J. Digest. Dis. **3**:15-17, 1936. Ruffin, J. M., and Reeves, R. J.: The Value of Gastroscopy in the Diagnosis of Phytobezoar, ibid. **5**:745-746, 1939. (*c*) Browne, D. C., and McHardy, G.: Gastroscopy and Phytobezoar: Report of Case of Diospyrobezoar, Arch. Int. Med. **65**:368-374 (Feb.) 1940. (*d*) Patterson, C. O., and Rouse, M. O.: Foreign Bodies in the Stomach Observed Through the Gastroscope, Texas State J. Med. **36**:238-242, 1940. (*e*) Cohn, A. L., and White, A. S.: Gastroscopic Diagnosis of Phytobezoar, Am. J. Surg. **51**:432-435, 1941.

3. Lawrie, E. S.: A Case of Persimmon Bezoar, J. Malaya Br., Brit. M. A. **3**:190-193, 1939.

4. McCarley, T. H., and Greenberger, E. D.: Persimmon Phytobezoar Mistaken for Gastric Cancer, Radiology **36**:232-233, 1941.

5. Kooyker, H. A.: Zur Casuistik der Gastrolithen beim Menschen, Ztschr. klin. Med. **14**:203-211, 1888.

6. Izumi, S.; Isida, K., and Iwamoto, M.: The Mechanism of Formation of Phytobezoars, with Special Reference to Persimmon Ball, Jap. J. M. Sc. Tr., II, Biochem. **2**:21-35, 1933.

7. Hart, W. E.: Phytobezoars, J. A. M. A. **81**:1870-1875 (Dec. 1) 1923.

8. (*a*) Hart.[7] (*b*) Crossan, E. T.: Phytobezoar with Gastric Ulcer, Ann. Surg. **101**:1451-1452, 1935. (*c*) Chont, L. K.: Phytobezoar and Its Formation in Vitro, Radiology **38**:14-21, 1942.

symptom complex was noted even in this case, although there were symptoms also of postoperative stenosis, complicating the clinical findings.

Although there are reports in the literature of 4 cases in which a phytobezoar apparently came from a stomach, which had been operated on, the foreign body has never been directly observed at this site. On 1 occasion,[9] the stomach had been partially resected according to the method of Reichel and Polya because of a phytobezoar of five weeks' duration, associated with two gastric ulcers. Nine months later, obstruction developed high in the intestine, and another bezoar 6.5 by 8 cm. and weighing 120 Gm.—apparently newly formed in the resected stomach but perhaps only a part of a double bezoar overlooked at the first operation—had to be removed from the jejunum, 3 inches (7.5 cm.) distal to the anastomosis. In another case,[10] obstruction of the jejunum by a persimmon ball was observed; three months before, pyloric resection and end to end anastomosis with the duodenum had been performed because of the presence of an ulcer and the suspicion of malignancy, but apparently the foreign body had been overlooked and left in the stomach at the first operation. In the third case,[7] the patient had a gastroenterostomy and was operated on for intestinal obstruction; a cylindrical foreign body 5 by 7.5 cm. was removed from the jejunum, a few inches from the anastomosis. Even in the fourth case,[11] in which the patient had a gastroenterostomy, a phytobezoar 12 cm. in diameter and weighing 126 Gm. was removed from the intestine, 1 mm. distal to the anastomosis. All 4 patients recovered. Artificial anastomoses seem to favor the passage of especially voluminous masses, which regularly become fixed in the upper portion of the jejunum; the postoperative results in this complication, however, have been good. Except in cases in which the anastomosis is very narrow, a phytobezoar in a stomach which has been operated on should be removed surgically without much delay. As for the present case, with a stenotic anastomosis, expectation was correct. In the stomach which has not been operated on, on the contrary, if a phytobezoar passes the pylorus and becomes fixed, it is usually in the distal portion of the ileum; in 34 cases, only 7 exceptions were noted, the foreign body being fixed

9. Binotto, A.: Contributo allo studio dei corpi estranei del canale gastroenterico, Gior. veneto di sc. med. **13**:445-462, 1939.

10. Bullock, W. O.; in discussion on Griffith, F. W.: Obstruction of Small Intestine Due to Food Products, Ann. Surg. **103**:769-772, 1936.

11. Peronato, G.: Fitobezoari dello stomaco, del tenue, del colon, Arch. ital. di chir. **61**:174-194, 1941 (bibliography).

in the duodenum[12] or the jejunum.[13] In cases in which the stomach has not been operated on, the obstructions caused by Diospyros virginiana have occurred in the ileum close to the cecum, whereas those caused by the Japanese variety of the same plant (in whatever part of the world) have been in the upper portion of the small intestine, from the duodenum to the jejunum; apparently the size of a bezoar is not the only factor determining the site of an obstruction.[14]

The case material on phytobezoar shows no arguments against clinical expectation in suitable cases. (Agglomerations of vegetable material in the stomach have been called phytobezoars without account for the duration. No well defined criteria exist as to those removed from the intestine. A great number of agglomerations leave the stomach some hours or days after being formed, usually during the first hours; these have been called "food boli" in the literature. Others enter the intestine not before some weeks, months or years after ingestion. When a long time passes between ingestion and intestinal obstruction, the case is usually recorded as one of phytobezoar. Two cases were listed as cases of phytobezoar by some authors,[15] and as cases of food boli, by others.[16] Unchewed masses of ingesta[17] should be differentiated from real phytobezoars and food boli.) Except for an undiagnosed case of the preroentgen period, a complication has developed in a hospital in only 2 cases: In the first, intestinal obstruction and peritonitis developed in a patient hospitalized after childbirth; she recovered after the removal of a foreign body 2 cm. in diameter from the intestine at the site of an old adhesion.[18] In the second, ileus of four days' duration was followed by spontaneous recovery and passing of a phytobezoar in a child operated on for another intestinal obstruction by a bezoar fourteen days before.[19]

12. (*a*) Izumi, Isida and Iwamoto.[6] (*b*) Langenbuch: Demonstration eigenthümlich grosser Concretionen des Magens und des Dünndarms, welche durch Enterotomie herausgefördert worden sind, Verhandl. d. deutsch. Gesellsch. f. Chir. **9**:54, 1881. Yeo, G., cited by Peronato.[11]

13. (*a*) Izumi, Isida and Iwamoto.[6] (*b*) Lobinger, A. S., cited by Hargrave, R. L., and Hargrave, R.: Acute Intestinal Obstruction by Persimmon Phytobezoar: Report of Two Cases, Ann. Surg. **104**:65-73, 1936. (*c*) Newburger.[14]

14. Newburger, B.: Intestinal Obstruction Due to Phytobezoar, Rev. Gastroenterol. **8**:293-300, 1941 (bibliography).

15. Lobinger.[13b] Simpson, B. S.: Intestinal Obstruction by Unusual Form of Enterolith, Edinburgh M. J. **30**:176-178, 1923.

16. (*a*) Caylor, H. D., and Nickel, A. C.: Intestinal Obstruction from Food Bolus, Ann. Surg. **104**:151-154, 1936. (*b*) Elliot, A. H.: Intestinal Obstruction Caused by Food, Am. J. M. Sc. **184**:85-94, 1932.

17. Obstruction of Small Intestine, Cabot Case 28212, New England J. Med. **226**:864-866, 1942.

18. Downing, W.: Obstruction and Perforation of Small Intestine Due to Coprolith, J. A. M. A. **86**:550 (Feb. 20) 1926.

19. Hibi, H.: Phytobezoar, Nippon Shokakibyo Gakkai Zasshi **26**:27-32, 1927.

Since one must be prepared to meet complications an analysis of the literature on their occurrence and therapy is important. There is evidence of a number of unreported instances of the spontaneous disappearance of a phytobezoar; the literature probably gives a one-sided view. A notion of the frequency of disappearance may be obtained from table 3, which contains data on the cases of food boli in the literature [20] for comparison. The material up to 1938 has previously been collected [20c]; references not given in the present article are to be found in that bibliography. Reports on 44 additional cases have appeared in the recent literature.[21] The prognosis is probably generally

TABLE 3.—*Complications in 130 Cases of Phytobezoar and 28 Cases of Food Bolus**

Time After Ingestion	Uncomplicated Cases (Operated on or Healed Spontaneously)	Intestinal Obstruction and Perforation	Ulcer Perforation	Gastric Bleeding
12 hours	..	.. (14)†	1‡	..
2 days	..	1 (9)	..	..
3- 7 days	3	5 (3)	..	..
1- 2 weeks	5	3 (1)	..	1
2- 4 weeks	14	1	1	..
1- 2 months	9	1 (1)	2	2
2- 3 months	10	2	..	1
3- 6 months	13	2	..	1
6-12 months	20	5	1	..
1- 2 years	11	1	..	..
2- 5 years	7	2	1	1
5-11 years	2	..	..	1

* Figures in parentheses represent the number of cases of food bolus.
† In 1 case the food bolus measuring 1½ by 2½ inches (3 by 6 cm.) was vomited.
‡ This was a case of gastric rupture in child aged 3 years.

20. (*a*) Caylor and Nickel.[16a] (*b*) Elliot.[16b] (*c*) DeBakey, M., and Ochsner, A.: Bezoars and Concretions, Surgery **4**:934-963, 1938; **5**:132-160, 1939 (bibliography). (*d*) Latchmore, A. J. C.: Stomach-Ache, Lancet **1**:1153-1155, 1940.

21. (*a*) Walk.[1] (*b*) Footnotes 2, *b*, *c*, *d* and *e*, 3 and 4. (*c*) Chont.[8c] (*d*) Binotto.[9] (*e*) Peronato.[11] (*f*) Newburger.[14] (*g*) Bernardes de Oliveira, A.: Dois casos rares de cirurgía gástrica: fitobezoar; adenoma do estômago, Rev. de cir. de São Paulo **7**:197-222, 1941. (*h*) Cambel, P., and Konuralp, H. Z.: Ueber Hortobezoare in der Türkei und zwei eigene Fälle bei Magenkarzinom, Zentralbl. allg. Path. u. path. Anat. **80**:245-248, 1943. (*i*) Cavusoglu, E., cited by Cambel and Konuralp.[21h] (*j*) Gürkan, K. J.: Phytobezoar-Fall mit interessantem radioskopischem Befund, Chirurg. **15**:554-555, 1943. (*k*) Hancock, J. C.: Japanese Persimmon Bezoars, J. Iowa M. Soc. **28**:234-238, 1938. (*l*) Hirsch, D. J., cited by Groves in discussion on White.[21v] (*m*) Hoge, A. F.: Phytobezoar, J. Arkansas M. Soc. **39**:157-159, 1942. (*n*) Lyons, C. G., and Cody, G. L.: Bezoar, Radiology **31**:225-239, 1938. (*o*) Maes, U., in discussion on White.[21v] (*p*)

better than might appear from the following analysis of the literature, which contains reports even on patients admitted for treatment late and in poor condition.

Intestinal Obstruction.—This has most frequently developed during the first twelve hours and in a great number of cases during the first two days after ingestion. The risk of this complication has diminished on the third day. It is slight but still present after the second week, and obstruction has even occurred two years after ingestion.

The literature on this complication was recently summarized.[14] The mortality of 40 per cent can probably be considerably reduced if the complication should develop while the patient is being treated in the clinic and is treated in good time. Roentgen examination in case of an acute abdominal condition, hitherto used in 2 cases,[22] permits a better diagnosis than do clinical symptoms only. Even in cases of spontaneous passing of a phytobezoar there may be temporary signs of intestinal obstruction.[23] An obstruction may be incomplete [24] but followed by ulceration of the intestinal wall and perforation.[24b] The foreign body may remain in the intestine, clinically resembling a tumor [25] or an appendical abscess.[26] At operation for an intestinal obstruction even the stomach should be palpated; another bezoar was thus detected in the stomach in some cases [27] and in others was overlooked there.[28]

Gastric Ulcer, Perforation and Hemorrhage.—Gastric ulcer has been recorded in 39 cases of phytobezoar. Its presence apparently does not alter the therapy as far as it concerns the foreign body.

McNeill, J. H.: Persimmon Phytobezoar with Case Report, Ann. Int. Med. **14**:2412-2417, 1941. (*q*) Parzani, C.: Sui corpi liberi della cavità gastrica, Gior. veneto di sc. med. **12**:32-36, 1938. (*r*) Rachlin, S. A.: Intragastric Benign Tumor Associated with Penetrating Ulcer of Lesser Curvature, M. Bull. Vet. Admin. **19**:113-114, 1942. (*s*) Ramstad, N. O.: Phytobezoar with Gastric Ulcer, Journal-Lancet **58**:505-506, 1938. (*t*) Serck-Hansen, T.: Phytobezoar, Med. rev., Bergen **55**:171-174, 1938. (*u*) Snelling, J. G., cited by Graves, in discussion on White.[21v] (*v*) White, R. J., Persimmon Phytobezoar, South. M. J. **31**:750-756 1938. (*w*) Woolsey, R. A., in discussion on White.[21v]

22. Newburger.[14] De Bakey and Ochsner.[20c]

23. (*a*) Hibi.[19] (*b*) DeBakey and Ochsner.[20c] (*c*) Hichens, P. S., and Odgers, N. B.: A Case of Vegetable Gastrolith, Brit. M. J. **1**:606-607, 1912.

24. (*a*) Cited by Newburger.[14] (*b*) Tosatti, cited by Peronato.[11]

25. Lagoutte, cited by Peronato.[11]

26. Murdock, H. D.: Persimmon Bezoars Occurring Around Tulsa, Oklahoma, J. Oklahoma M. A. **27**:442-447, 1934.

27. Hart.[7] Langenbuch.[12b] Murdock.[26] Balfour, D. C., and Good, R. W.: Phytobezoar Associated with Gastric Ulcer, Am. J. Surg. **6**:579-587, 1929. Good, R. W.: Phytobezoar, Proc. Staff Meet., Mayo Clin. **3**:237, 1928.

28. Moersch and Walters.[2b] Hibi.[19] DeBakey and Ochsner[20c] Hirsch.[21l] Maes.[21o]

The question arises as to the most rational handling of an ulcer in a patient operated on for phytobezoar. In 4 cases [29] partial resection of the stomach was carried out; in 2, excision of the ulcer,[30] and in 2, gastroenterostomy [8]; in an additional case, the ulcer was slightly cauter-

TABLE 4.—*Late Results in Cases of Phytobezoar Associated with Gastric Ulcer*

Author	Duration of Observation	Sex	Age	Gastric Symptoms Before Bezoar	Therapy	Ulcer	Results
Smith (1933) case 2	27 mo.	M	53	Chronic cholecystitis and disease of appendix	Operation	Large ulcer on lesser curvature penetrating into pancreas, inoperable	Dull pain at umbilical level not relieved by food or alkalis; roentgenograms showed no ulcer; considered chronic cholecystitis
Crossan (1935)	3 mo.	M	42	None	Operation	Saddle ulcers on lesser curvature, each 2 cm. in diameter	Well except for a few attacks of nausea
Moersch and Walters (1936)	4 mo.	M	49	None	Operation	Small healed ulcer on lesser curvature	Free of all symptoms after operation
Rutledge (1937)	4 mo.	M	24	None	Operation	Large penetrating prepyloric ulcer	Free of gastric symptoms
Satterfield (1937)	4 mo.	M	53	Appeared 13 years previously; recovered	Operation	3 prepyloric ulcers, the largest 4 by 4 cm.	No digestive symptoms
Allen (1938) case 1	9 mo.	M	71	Ulcer antedating phytobezoar?	Operation (twice)	Scar at pylorus; no ulcer at second operation	Good health reported
DeBakey and Ochsner (1938) case 7	Not stated	M	59	None	Operation	On greater curvature 2.5 cm. in diameter	Completely relieved of all complaints; roentgenograms showed no ulcer
White (1938) case 1	10 mo.	M	48	.....	Operation	1.5 cm. in diameter 7.5 cm. above pylorus	Gastric trouble 6 weeks postoperatively; recovered; perfectly well (table 2)
White (1938) case 2	9 mo.	M	46	.....	Operation; cauterization	Fresh ulcer on lesser curvature	Recovered; perfectly well ever since
Ramstad (1938)	2½ mo.	F	38	Operation for gallstones	Operation	2 cm. in diameter involving only the mucosa	No gastric distress; roentgenograms showed no ulcer
Walk (1940)	3 yr.	F	57	None	Conservative	0.5 cm. in diameter at angulus	Complete recovery after spontaneous disappearance of bezoar (table 1)
McNeill (1941)	1 yr.	M	57	.....	Excision of ulcer	1 by 2 cm. on greater curvature	No complaints after operation
Hoge (1942)	3 mo.	M	61	Ulcer antedating bezoar	Resection	2 cm in diameter deep in middle part of stomach	No more symptoms

ized.[21v] All the patients recovered. In 21 cases the ulcer was left untouched at operation. This group apparently included even patients

29. Binotto.[9] Hoge.[21m] Balfour, D. C., and Good, R. W.: Phytobezoar Associated with Gastric Ulcer, Am. J. Surg. **6**:579-587, 1929. Good, R. W.: Phytobezoar, Proc. Staff Meet., Mayo Clin. **3**:237, 1928.

30. (*a*) McNeill.[21p] (*b*) Potter, R. P.: Phytobezoar, Radiology **15**:685-688, 1930.

in poor condition. There were 3 deaths from pneumonia [31] and 1 from peritonitis.[32] Late results have been recorded in 13 cases in the literature (table 4). They were good; even large ulcers can thus safely be left untouched at the gastrotomy for removal of the foreign body. The opinion that most gastric ulcers in phytobezoar are decubital is thus supported by the late results, which apparently have not been analyzed before. When the results are compared with those in 11 cases without ulcer,[33] the difference is less than might be expected. In this group, occasional residual sensations of gastric distress were noted on one occasion.[7] Partial resection of the stomach is thus indicated only when the ulcer has been present and resistant to therapy before the appearance of the bezoar or when special morphologic features (fixation to extragastric organs, penetration to the liver or pancreas or risk of stenosis) demand radical surgical measures. Independent ulcer, not caused by the bezoar, has probably been observed in the duodenum as well as in the stomach.[34] When an operation is performed for phytobezoar, an independent ulcer probably can be handled as in cases of ordinary ulcer, without the special conservativism needed in the therapy of decubitus ulcer.

Perforation has occurred in cases of gastroduodenal ulcer without periods of predilection (table 3). In 1 case there was a duodenal ulcer [34b] and in the remaining 5 a gastric ulcer located in the prepyloric area,[34b] 6 cm. proximal to the pylorus [8c] or on the lesser curvature, the exact site not being stated.[35] No perforation has hitherto been observed in ulcer of the greater curvature.[36] In the surgical cases [37] the mortality from peritonitis was 40 per cent. Acute perforation of the

31. Brown and McHardy.[2e] Chont.[8c]

32. David, V. C.: Pseudocarcinoma of the Stomach, Ann. Surg. **87**:555-565, 1928.

33. (*a*) Patterson and Rouse.[2d] (*b*) Lawrie.[3] (*c*) Hart.[7] (*d*) Hancock.[21k] (*e*) Smith, L. A.: Hematemesis from Phytobezoar, Am. J. Surg. **22**:565-567, 1933. (*f*) Capelle: Concrétion gastrique, J. méd. de Brux., 1861, p. 147. (*g*) Garrett, D. L.: Phytobezoar Diospyri Virginianae: Case Report, J. Oklahoma M. A. **21**:64, 1928. (*h*) Porter, W. B., and McKinney, J. T.: Phytobezoar Diospyri Virginianae, Am. J. M. Sc. **72**:703-706, 1926. (*i*) Wyatt, W. S.: Phytobezoar, Kentucky M. J. **30**:79-80, 1932. (*j*) Thorek, P., and Rutter, C.: Trichobezoar and Phytobezoar, Am. J. Surg. **35**:603-606, 1937.

34. (*a*) Hart.[7] (*b*) Allen, L. G.: Phytobezoar, Am. J. Roentgenol. **39**:67-74, 1938.

35. Chont.[8c] Murdock.[26]

36. DeBakey and Ochsner.[20c] McNeill.[21p]

37. Chont.[8c] Murdock.[26] Allen.[34b]

anterior wall of the stomach during the first twelve hours after ingestion was noted in a child of 3 years.[38]

Gastric hemorrhage occurred in 7 cases of various durations (table 3). Sometimes slight,[2e] on other occasions it caused anemia,[39] and hemoglobin values of 30 to 41 per cent were recorded.[40] The treatment has been conservative. Operated on as soon as the general condition improved, 6 patients recovered [41]; on 1 occasion death from bronchopneumonia and pleural effusion occurred.[8c]

Emaciation.—Emaciation, with or without anemia, has been observed in long-standing cases [42]; it has even developed in one or two months [43] and has sometimes been associated with dehydration [44]; in cases in which operation has been performed after clinical treatment, which in some cases has lasted for twenty-six days, all patients have recovered. The results have thus been favorable. Grave emaciation, finally leading to death, has been observed in an undiagnosed case of the preroentgen period.[5]

For comparison, the mortality in 46 uncomplicated cases of phytobezoar in the stomach in which operation was performed was 4.3 per cent.[45]

SUMMARY

A unique case of phytobezoar in the stump after resection of the stomach is reported.

Not infrequently a phytobezoar disappears spontaneously. If its duration in a stomach not operated on does not exceed four weeks and if no complications demand immediate surgical intervention, the patient should be observed in the clinic and the operation postponed. The therapy of phytobezoar in a stomach on which operation has been done (with a gastroenterostomy or resection anastomosis) is different.

38. Herzog, M. A.: A Peculiar Gastrolith Leading to Perforation and Death, Tr. Chicago Path. Soc. **4**:162-164, 1899-1901.

39. (*a*) Patterson and Rouse.[2d] (*b*) McCarley and Greenberger.[4] (*c*) Chont.[8c] (*d*) DeBakey and Ochsner.[20c] (*e*) Smith.[33e] (*f*) Satterfield, W. T.: Phytobezoar, Memphis M. J. **12**:140-143, 1937.

40. Patterson and Rouse.[2d] McCarley and Greenberger.[4] Chont.[8c]

41. Patterson and Rouse.[2d] McCarley and Greenberger.[4] DeBakey and Ochsner.[20c] Smith.[33e] Satterfield.[39f]

42. Chont.[8c] Hamdi, H.: Drei Horto- oder Phytobezoarfälle beim Menschen, Deutsche med. Wchnschr. **52**:2122-2123, 1926.

43. Patterson and Rouse.[2d] Murdock.[26]

44. Rodgers, F. D.: Phytobezoar of Persimmon Origin, Radiology **29**:494-498, 1937.

45. Hart.[7] Outten, W. B.: Case of Double Gastrolith Removed by Gastrotomy, M. Fortnightly **6**:445-452, 1894.

A phytobezoar in such a stomach should be removed surgically without much delay because of the great risk of obstruction high in the intestine. Expectation of spontaneous disappearance is here justified only if the anastomosis is very narrow. As far as I know, this fact has not been pointed out in the literature.

Late results in cases of phytobezoar show remarkably good healing of a gastric ulcer after the disappearance or removal of the foreign body. Even a large ulcer can thus be left untouched at the operation for removal of the foreign body. Only when an ulcer is evidently independent of the bezoar, as observed on rare occasions, is the indication for gastric resection the same as for ordinary ulcer.

News and Comment

THIRD ANNUAL CLINICAL SESSION OF THE AMERICAN MEDICAL ASSOCIATION

The Third Annual Clinical Session of the American Medical Association will be held in Washington, D. C., December 6 to 9.

The Clinical Session will provide a full scale scientific program specifically designed for the general practitioner. Outstanding physicians will discuss such subjects as diabetes, pediatrics, laboratory diagnosis, physical medicine and rehabilitation, arthritis, dermatology, roentgen ray diagnosis, cancer and poliomyelitis. Coordinated with this outstanding scientific program will be approximately one hundred scientific exhibits which will present original work on the subjects discussed.

The newest offerings of one hundred and twenty-five manufacturing firms will comprise the Technical Exhibition. Here will be found the latest developments in scientific medical research, drugs and equipment.

Televised surgical and clinical procedures, similar to those shown in color at the Annual Session of the American Medical Association in Atlantic City last June, will be presented at the Washington meeting. The demonstrations will originate in the Johns Hopkins Hospital and will be shown on screens in the Armory. The television schedule will be spread over four days.

The House of Delegates will meet at the Hotel Statler during this session. One of the first orders of business will be the annual selection of the general practitioner who has made an exceptional contribution of service to his community.

An entertainment program is being planned for attending physicians and their wives. The highlight of this program will be on Wednesday evening, December 7, when the Philip Morris Company will originate its "This Is Your Life" broadcast from the Hotel Statler. The radio program will be followed by a stage show, in which outstanding stars will participate.

Blanks for hotel reservations and advance registrations may be found in *The Journal of the American Medical Association.*

International Symposium on High Altitude Biology.—In accordance with a resolution passed by the United Nations Educational, Scientific and Cultural Organization (UNESCO), an International Symposium on High Altitude Biology will take place in Lima, Peru, from Nov. 23 to 30, 1949 under the auspices of UNESCO and the government of Peru, the latter having appointed the Executive Committee of the Institute of Andean Biology as organizing committee for the symposium. Further information may be obtained from Dr. Carlos Monge M., Institute of Andean Biology, Post Office Box 821, Lima, Peru.

Urology Award.—The American Urological Association offers an annual award of $1,000 (first prize, $500; second price, $300, and third prize, $200) for essays on the result of clinical or laboratory research in urology. Competition is limited to urologists who have been in such specific practice for not more than five years and to residents in urology in recognized hospitals.

The first prize essay will appear on the program of the forthcoming meeting of the American Urological Association, to be held at the Hotel Statler, Washington, D. C., May 29 to June 1, 1950.

Further information may be secured from the secretary, Dr. Charles H. de T. Shivers, Boardwalk National Arcade Building, Atlantic City, N. J. Essays must be in his hands before Feb. 20, 1950.

Chicago Society of Internal Medicine.—At the annual meeting of the Chicago Society of Internal Medicine held May 23, 1949, the following officers were elected: president, Sidney Strauss; vice president, Howard L. Alt, and secretary-treasurer, Ernest G. McEwen.

Book Reviews

Synopsis of Pediatrics. By John Zahorsky, M.D., assisted by T. S. Zahorsky, M.D. Fifth edition. Price, $5.50. Pp. 449. St. Louis: C. V. Mosby Company, 1948.

Pediatrics includes the growth and development, congenital deformities, all types of trauma and diseases of the young. Therefore condensing all pediatric knowledge into one small volume is admittedly a difficult task. "Synopsis of Pediatrics" was prepared primarily for medical students and general practitioners. Its sixty-two chapters roughly correspond to the sixty hours devoted to didactic pediatrics in the St. Louis University School of Medicine. The author has spent a long professional life in the practice and teaching of pediatrics. The textbook is written from a practical clinical point of view, with major emphasis on office and home diagnosis and treatment. Much less emphasis is placed on the more complicated procedures of the hospital and laboratory.

The first nine chapters are devoted to feeding, growth and nutrition. They represent present day knowledge and opinions prevailing in the pediatric profession. Chapters XII to XVIII are devoted to derangements of growth and nutrition. Chapters XIX to XXXIII are a condensed practical description of the infectious diseases of childhood with current therapeutic procedures including a discussion of chemotherapy and the antibiotics.

The remainder of the text is divided into descriptions of diseases according to anatomic systems and special organs. There are six chapters on diseases of the gastrointestinal tract and seven on those of the respiratory organs. This properly emphasizes the fact that most diseased conditions encountered in pediatric practice are centered in these organs. Five chapters describe functional diseases and pathologic changes of the nervous system. The author does not emphasize the psychiatric aspect in proportion to present day pediatric trends. Diseases of other systems and special organs such as the genitourinary system, skin, eye and ear are briefly described.

In summary, the volume gives a brief but rather comprehensive description of all the common diseases and conditions met in pediatric practice. At least some statement is made concerning most of the uncommon and rare pediatric diseases. The volume will serve as a textbook for medical students and a handbook for medical men in general.

Hemolysis and Related Phenomena. By Eric Ponder, M.D. Price, $10. Pp. 398, with 69 illustrations. New York: Grune & Stratton, Inc., 1948.

Of the 400 pages in this monograph, only a small share are applicable to the clinical problems of the hemolytic diseases. The balance is a most thorough presentation of the current status of the unique characteristics of the mammalian erythrocyte. The material is presented in a critical and scholarly manner and in great detail. It is fascinating for the reviewer—a clinician—to contemplate the amount of research in general physiology devoted to the red cell. In his introduction, Dr. Ponder says that he has been accused of speaking of the red cell as if it

were a microcosm, an understanding of which would include an understanding of nearly everything else in the cellular world. He points out aptly that "lysis is a special, if somewhat extreme case of altered permeability; the actions of lysins on red cells is a special case of the action of drug-like substances, the osmotic properties of the erythrocyte is a special case of osmotic behavior in general, and so on." He asks, correctly, how we can expect to understand these and other phenomena in complex cells, such as muscle, nerve and gland cells, and he could add neoplastic cells, if we are unable to understand them in the case of the relatively simple, symmetric and inactive erythrocyte. This monograph requires a considerable effort to read, and the general reader may be dismayed by the mathematical formulas and allusions to unfamiliar physical chemical concepts. The presentation, however, is lucid, and the arguments are so well presented that a lack of knowledge of calculus is no bar to an understanding of the material.

The reviewer closed the book with a better appreciation of the complexities of cellular physiology and a greater sympathy for the fundamental scientists who work at the very limits of our present knowledge. The typical complacency of the practical man who feels that he has interpreted a process because he has described it is healthily disturbed by a monograph of this type.

Vitamin A Requirement of Human Adults: An Experimental Study of Vitamin A Deprivation in Man. A Report of the Vitamin A Sub-Committee of the Accessory Food Factors Committee. Compiled by E. M. Hume and H. A. Krebs. Medical Research Council Special Report Series, No. 264. Price, 3s. Pp. 145. London: His Majesty's Stationery Office, 1949.

This monograph is a description of a long and complicated experimental study on 23 human volunteers, 16 of whom were given a diet virtually devoid of vitamin A and carotene; the remaining 7 received the same diet with a daily supplement of either 2,500 international units of oleovitamin A U. S. P. (natural vitamin A in oil), or 5,000 international units of carotene. The principal laboratory tests used to determine the extent of vitamin A deficiency were measurements of plasma vitamin A and carotenoid content and various tests of retinal function. The latter were the more reliable. Indisputable evidence of deficiency did not appear until after eight months; ultimately, unmistakable deficiency developed in only 3 of the 16 volunteers who persisted in the tests for twelve to twenty-four months.

Follicular hyperkeratosis, conjunctival degeneration and abnormal fatigue were not encountered. After deficiency states were observed, the amounts of vitamin A or carotene required to treat them were studied. The final conclusion was that 2,500 international units of vitamin A or 7,500 international units of carotene represented the daily requirement for adults. This value is in close agreement with that in the schedule of the National Research Council's Committee on Food and Nutrition.

Carefully conducted studies such as this are extremely useful to the clinician who seeks to evaluate the claims of the vitamin salesmen. The subjects of the experiment were healthy young adults, and it is obvious that similar results would not have been obtained had children, pregnant women or chronically undernourished persons been studied. However, it is good to know how great is the delay before the onset of symptoms of vitamin deficiency. The reserve stores of vitamin A

known to be present in the liver were apparently sufficient to maintain normal retinal function for a period of two hundred to four hundred days. This appears to be a good measure of the adequacy of the average unsupplemented British diet. It is hard to believe that the average American diet is less adequate.

The Rh Blood Groups and Their Clinical Effects. By P. L. Mollison, A. E. Mourant and R. R. Race. Medical Research Council Memorandum No. 19. Price, 1s. 6d. Pp. 74. London: His Majesty's Stationery Office, 1948.

Just ten years ago, Levine and Stetson discovered an atypical immune agglutinin in the serum of a woman after stillbirth. In 1940, Landsteiner and Wiener discovered a new antigen in erythrocytes, which they called Rh. Subsequently, it was demonstrated that immune body reactions were responsible for certain hemolytic reactions in transfusions and for the occurrence of erythroblastosis fetalis. The Rh groups were studied intensively by American and British workers, under the stimulus of the wartime expansion of blood transfusion services. The genetic relationships of the various Rh groups were anticipated, and, in fact, several genotypes were predicted prior to their actual discovery.

In 1943 the British geneticist, R. A. Fischer, made a theoretic analysis of the problem and concluded that the presence of three closely linked genes in one pair of chromosomes could explain the observations. These he designated C, D and E. It is possible to specify the genetic and antigenic constitution of any person in these terms, e. g., cde/cde (Rh negative) and cDe/cDe (Rh positive). In the United States, the genetic constitution is usually indicated by the "short symbol" of Wiener and his associates, e.g., rr and Ro Ro. In spite of the complexity of these two systems, it is obvious that the well trained internist must have at least a working knowledge of this revolutionary subject.

This Medical Research Council memorandum is the most authoritative and easily understandable summary of present knowledge available on this subject. The first section, by Race, is an admirable and concise presentation of the Rh groups, the different Rh antibodies and the genetic basis of the Rh groups. The second section, by Mollison, is devoted to clinical consideration as related to blood transfusions and the management of erythroblastosis fetalis.

The final section, by Mourant, describes in detail approved methods for Rh testing, the circumstances in which the tests should be applied and the proper interpretation of them.

At the present time, it is accepted that the transfusion of incompatible blood is a grave mistake, except in dire emergencies. This 74 page memorandum provides all the information necessary to appreciate the importance of the Rh groups and to manage properly the Rh negative patient. It is highly recommended for all concerned with blood transfusions and with pregnant women.

Cardiovascular Disease in General Practice. By Terence East, M.A., D.M. (Oxon.), F.R.C.P. (London). Third edition. Price, 15s. Pp. 218, with 34 illustrations. London: H. K. Lewis & Company, Ltd., 1949.

This small booklet is planned for the general practitioner, and it contains most practical material. Its aim is to give clear, succinct and practical information. "seasoned with sane comment." The commonest heart diseases and disorders are described briefly in the twenty-one chapters, some of them being just mentioned

in a few words. New advances of medicine are also included. Electrocardiography has been omitted with purpose, because "a little learning is a dangerous thing."

The author describes, in clear and simple style, the nature of each disorder, its clinical picture and diagnosis, prognosis and treatment. General treatment is condensed in a special chapter. There are several drawings, illustrating different shapes of the heart, etc.

This book can be recommended as a time saver.

More Than Armies: The Story of Edward H. Cary, M.D. By Booth Mooney, M.D. Price, $5. Pp. 270. Dallas, Texas: Mathis, Van Nort & Co., 1948.

This is an excellent medical biography. Here is unfolded the story of one of medicine's elder statesmen, Dr. Edward Henry Cary, a distinguished ophthalmologist, a former president and trustee of the American Medical Association, founder and president of the Southwestern Medical Foundation, Chairman of the Board of the National Physician's Committee for the Extension of Medical Care and a member and high office holder in many medical societies and civic organizations.

Dr. Cary continually preached as well as practiced the adoption of the highest standards of education, of conduct and of medical service. He has steadfastly defended the American system of medical practice against any threat of federal or state bureaucracy or "political" control because of his conviction that such a change would not be in the best interest of either the people or the medical profession.

On Feb. 28, 1947, the occasion of his seventy-fifth birthday, the officers and trustees of the Southwestern Medical Foundation honored Dr. Cary with a dinner at which there were over five hundred citizens of Dallas and its environs and many leaders in medicine from the various states. Dr. Cary was lauded not alone for his natural endowments but also for the direction of his leadership. Dr. Morris Fishbein, editor of *The Journal of the American Medical Association*, gave the principal address and in summation said: "This man is a physician, a distinguished scientist, a medical statesman, a great builder, an educator, an idealist—all combined in the person of one dynamic, driving, courageous and at the same time gentle, friendly and affectionate human being."

The author brings this biography to a close with the following statement: "Dr. Cary has built his own enduring monument and lived to see that it is good. A man could hardly ask for more."

An Introduction to Cardiology. By Geoffrey Bourne, M.D., F.R.C.P. Price, $4.50. Pp. 264, with 64 illustrations. Baltimore: Williams & Wilkins Company, 1949.

This little book does not seem to add much to what is already available in textbook form. On the whole, the concise statements are adequate, and the numerous reproductions of electrocardiograms and roentgenograms are helpful. It is of interest that the classic prescription for the treatment of auricular flutter, long since thought obsolete by many, is preserved. The book is extremely well written; the example of the old lady running around the lamppost (page 99) gives a good idea of what quinidine does in auricular fibrillation, although even the established concept of circus movement has recently been questioned.

The Digestive Tract in Roentgenology. By Jacob Buckstein, M.D. Price, $16. Pp. 889, with 1,030 illustrations. Philadelphia: J. B. Lippincott Company, 1948.

This volume is a summary of the information obtained by the author during twenty-five years of experience in correlating the roentgenographic findings with those obtained at operation and autopsy from an enormous amount of material. The author's previous book "Clinical Roentgenology of the Alimentary Tract" is well known and has served as a valuable textbook.

There are sixty-five chapters divided into the following nine sections: Introduction, the Hypopharynx and Esophagus, the Stomach, the Duodenum, the Small Intestine, the Large Intestine, Herniation and Eventration of the Diaphragm, the Gallbladder and Bile Ducts and the Spleen, Liver and Pancreas. The book is fairly comprehensive, and considerable space is devoted to the more common gastrointestinal lesions.

The technical procedures necessary for accurate examination are covered in detail. In each section the roentgen findings of the normal organ are discussed. The important clinical findings are integrated with the roentgen signs, and many illustrative case histories are included.

There are numerous excellent illustrations, and the text is clear, detailed and well written. This volume is a necessary addition to the library of every physician and surgeon interested in the gastrointestinal tract.

Clinical Aspects and Treatment of Surgical Infections. By Frank Lamont Meleney, M.D. Price, $12. Pp. 840, with 287 illustrations. Philadelphia: W. B. Saunders Company, 1949.

Dr. Meleney has written thoroughly on the subject of surgical infections. He speaks with authority, since he has been a surgeon for twenty-five years and, during this time, has been a pioneer in establishing the importance of integrating the bacteriologic laboratory with the surgical service.

The book contains a review of the so-called surgical infections as they affect various organs and tissues of the body. In addition to covering Dr. Meleney's own experience, the book contains chapters written by some of his colleagues at the Presbyterian Hospital, including Drs. Lockwood, Harvey, Longacre and Sandusky.

Correlated with the studies on surgical infections are descriptions of contributing etiologic factors and surgical therapy. The place of antibiotic therapy and the sulfonamide drugs in the treatment of infections has been considered in every phase of the subject. The last chapter deals with surgical infections in war wounds, and it is very interesting.

The book is an excellent addition to the library of any physician or surgeon and is equally valuable for medical students.

Mycoses and Practical Mycology. By N. Gohar. Price, $6. Pp. 234, with 134 illustrations. Baltimore: The Williams & Wilkins Company, 1949.

This book simplifies, for the student and the clinician, a difficult and neglected problem. It should prove extremely useful because it is brief, somewhat dogmatic and profusely illustrated. Therapy is simplified, and only the accepted methods are discussed. The volume is highly recommended.

The Uses of Penicillin and Streptomycin. By Chester S. Keefer, M.D. Price, $2. Pp. 72. Lawrence, Kan.: The University of Kansas Press, 1949.

The Porter Lectures for 1949, given under the auspices of the University of Kansas School of Medicine, appear under the imprint of the University of Kansas Press in a neat and attractive volume. The three lectures given by Dr. Chester S. Keefer deal with the uses of penicillin and streptomycin, as well as other antibacterial agents from microbes. No one is better fitted to discuss this subject than Dr. Keefer, and his precise and lucid summary of the subject makes interesting as well as useful reading.

Coronary Heart Disease. By A. Carlton Ernstene, M.D. Price, $2.50. Pp. 95. Springfield, Ill.: Charles C Thomas, 1948.

In this monograph the author presents in a readable form the elementary concepts of the subject of coronary heart disease. The various manifestations of the condition are considered from the standpoint of lesions present, clinical findings and treatment. The criteria presented for diagnosis and the methods of treatment outlined are widely accepted. The monograph has little to offer the advanced student or the practitioner who has any considerable contact with patients suffering from coronary heart disease. In the discussion on the electrocardiographic changes seen in coronary disease, the absence of figures illustrating such changes makes their visualization by the reader much more difficult.

Cardiac Catheterization in Congenital Heart Disease. By A. Cournand, M.D.; Janet S. Baldwin, M.D., and A. Himmelstein, M.D. Price, $4.00. Pp. 108. New York: Commonwealth Fund, 1949.

This brief monograph is based on an exhibit on the subject, previously presented by the authors. The material is clearly and concisely presented in relatively few pages. It is supplemented by many diagrams and illustrations. Theoretic data are presented in the initial pages, and the results of studies of actual cases in the remainder. The cyanotic group of congenital defects was intentionally omitted. This fine work is to be highly recommended to all persons interested in the problem. It is particularly useful to beginners, since it is written in a clear and simple fashion and includes detailed specifications of materials, technic and source of equipment for catheterization of the heart.

The Literature on Streptomycin 1944-1948. By Selman A. Waksman. Price, $3. Pp. 112. New Brunswick, N. J.: Rutgers University Press, 1948.

This volume, which consists of 1,171 references on streptomycin for the years 1944 to 1948, 12 references dealing with actinomyces and 16 with streptothricin, and which is indexed by author and subject, is not suitable for review.

Posttraumatic Epilepsy. By A. Earl Walker, M.D. Price, $2.75. Pp. 90, with 28 illustrations. Springfield, Ill.: Charles C Thomas, Publisher, 1949.

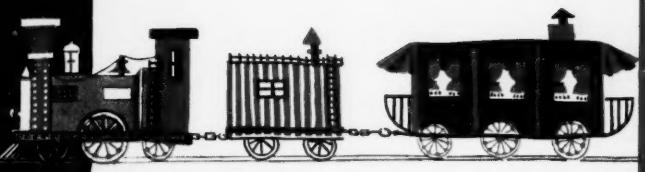
Although this little book contains an admirable discussion of all the features of the post-traumatic epilepsies, it is not unnatural that the author should be especially concerned with the surgical treatment of these disorders. His experience includes over 200 cases, and the results, both of medical therapy and of operation, are analyzed. The book is finely printed and illustrated; there are an index and a bibliography.

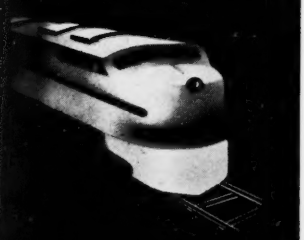
Symposium on Treatment of Long-Term Illness. The Medical Clinics of North America. Pp. 314, with 165 illustrations. Philadelphia: W. B. Saunders Company, 1949.

This volume follows the general familiar pattern of the others in the series. "Long term illness" means little from the standpoint of classifications, so one finds a great variety of conditions dealt with—for example, cardiac, pulmonary and hepatic disease. Most of the writers are authorities in their field, and have written good summary articles; the volume definitely makes interesting and useful reading.

A.M.A. Interns' Manual. Price, $2.25. Pp. 201. Philadelphia: W. B. Saunders Company, 1948.

This is a useful little book which should prove to be of value to the intern. Laboratory and clinical data, drugs and their dosage, materia medica, acute poisoning, diet and nutrition and physical medicine are among the subjects discussed. These problems are presented concisely and briefly in a small, easily portable handbook of 201 pages.





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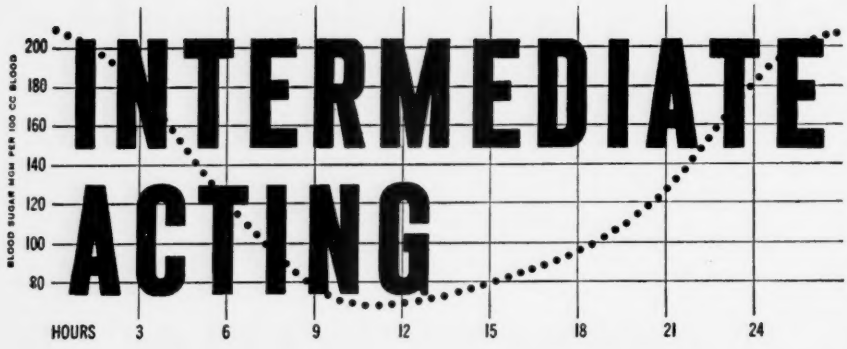

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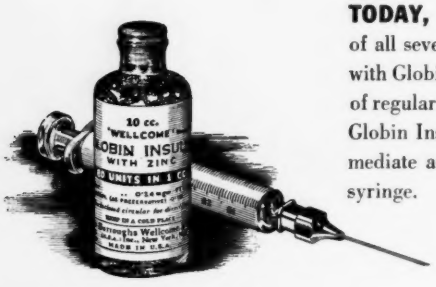

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1. Rohr, J.H., and Colwell, A.R.: Arch. Int. Med. 82:54, 1948.
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